Glucocorticosteroids

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Methyl prednisolone in anaphylactic shock bcoz non genomic effect is high.

1) classification of Glucocorticosteroids:

- Natural - Cortisone and hydrocortisone (cortisol)
Cortisone as a biologically inactive compound that in the liver develop into biologically active hydrocortisone.
- Semi Synthetic - Prednisone, methylprednisone, triamcinolone, dexamethasone, bethamethasone etc which are derivatives of hydrocortisone

* Semisynthetic GCs are divided into :-
- Non fluorinated (prednisone, methylprednisolone
- fluorinated (dexamethasone, triamcinolone, betamethasone).

- On the basis of duration of action it is classified as :- (Synthetic GCs).

1) Short acting ($T_{1/2}$ = 8-12 hr) - hydrocortisone cortisone.

2) Medium duration action ($T_{1/2}$: 18-36 hr) - prednisone Prednisolone, methylprednisolone.

3) Long acting - ($T_{1/2}$ - 36-54 hr) - Dexamethasone, betamethasone, triamcinolone.

* Inhalational - fluticasone, budesonide, beclamethasone.
* Topical - clobetasol, mometasone furoate.

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2) Pharmacokinetics of Glucocorticosteroids.

- When administered, GICs are rapidly and almost completely absorb in the upper Jejunum.
- Cmax in the blood is noted after 30-180 min.
- Food slightly reduces the rate of absorption but does not reduce its degree.
- In the blood GICs binds with albumen and transcortin (a corticosteroid - binding alpha 1- globulin).
- Natural GICs binds to protein in 90-97%. and Semi Synthetic in 40-60%.

As a results - a higher concentration in the tissue of semi synthetic GICs and their higher activity.

The degree of binding of GICs with serum protein also depends on the taken dose.

- With a low dose - protein binding ability is 80-90%.

High dose - 60%.

- Greater amount of free, non protein bound drug diffuses into peripheral tissues which rises the risk of side effects.
- Systemic absorption of GICs is also observed with their local (cutaneous) use and ranges from 30 to 90%.

- Skin absorption is increased in children, enhanced by application after washing, when applied to an affected skin or on parts of the body with thin skin.
- GCS penetrate well through the histohematological barriers, including through the BBB; pass through placenta.
- GCS undergo biotransformation in the liver with the formation of inactive metabolites (sulfates and glucuronides), after which they are excreted by the kidneys and only less than 15% of GCS are excreted unchanged in the urine.

3) Pharmacodynamics of Glucocorticosteroids.

- Variants of pharmacodynamic therapy of GCS:-
  - Local (intraarticular, rectal)
  - local (cutaneous, intranasal, inhalation, eye drops
  - Systemic - orally, parenterally (IV, IM), rectally
- For long term systemic therapy, oral administration of GCS is preferred
- Injectable forms of GCS with i/m and especially with i/v administration are rapidly metabolized and therefore their effect is short term and weaker than when taken orally, therefore in order to obtain an equivalent, compared with oral therapeutic effect, the dose of parenteral GCS should be 2-4 times higher than oral dose.

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Equivalent doses of GCS in mg :-
Hydrocortisone - 20 mg
Cortisone - 25 mg
Prednisolone - 5 mg
Methylprednisolone - 4 mg
Triamnisolone - 4 mg
Parametasone - 2 mg
Dexamethasone - 0.75 mg
Betamethasone - 0.6 mg.

Compared to prednisolone, methylprednisolone has a slightly higher GCS activity and has a weaker mineralcorticoid effects

Prednisone is hydroxylated in the liver where it turns into a metabolically active prednisone, and therefore is not recommended for severe liver disease.

Triamcinolone is deprived of mineral corticoid activity hence the lower ability to retain sodium and water compared to other GCS. Compared with prednisone, it has a more pronounced (by 20%) and prolonged GCS effect. On the other hand it often causes adverse drug reaction to the skin and muscle tissue and cause triamcinolone myopathy. Therefore prolonged use is undesirable.

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Dexamethasone

Glucocorticoid activity ca 7 times higher than prednisone's and does not have a mineralocorticoid effect. It suppresses the function of adrenal cortex to a greater extent.
For long term use it is not recommended due to danger of serious side effects (primarily, inhibition of the hypothalamic pituitary adrenal axis, metabolic defects, psychostimulating effects)

Betamethasone

Glucocorticoid activity is slightly higher than dexamethasone's and ca 8-10 times higher than prednisolone's.
For IV, IA and periarticular administration, a mixture of their two esters is used: Betamethasone-phosphate (absorbed quickly and provides an effect already after 30 minutes after administration) and dipropionate (absorbed slowly and provides a long lasting up to 4 weeks or more). This mixture is a micro crystalline suspension. That cannot be administered I/V.

Hydrocortisone

Hydrocortisone as well as Cortisone is not recommended for pharmacodynamic therapy as by GCS activity it is 4 times weaker than prednisolone and has a higher mineral corticoid activity (edema, hypertension, progression of

heart failure). It is mainly used for replacement therapy.
In acute adrenal insufficiency and other emergency condition, the DOC is hydrocortisone hemisuccinate.

4) Indication for glucocorticosteroids. Principle of dosage:
- Rheumatology (systemic vasculitis, arthritis)
- Transplantology (suppression of transplant rejection reaction)
- Hematology (immune hemolytic anemia, leukemia, lymphoproliferative disease)
- Allergology (urticaria, anaphylactic shock)
- Nephrology (glomerulonephritis)
- Gastroenterology (inflammatory bowel disease, liver disease)
- Pulmonology (bronchial asthma, respiratory distress syndrome)
- Ophthalmology (uveitis, allergic keratitis, acute optic neuritis).
- Endocrinology (autoimmune thyroiditis, Addison's disease, adrenogenital syndrome)
- Dermatology (bullous dermatoses, erythema nodosum, Eczema etc.
- Neurological Disease (multiple sclerosis, cerebro vasculitis, acute spinal cord injury etc)

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- Anesthesiology and resuscitation (prevention and treatment of shock: operating, traumatic, anaphylactic, burn, cardiogenic etc).

* Dose of GCS depends on the characteristics of the disease, inflammatory activity, risk factors for side effects and an individual response to this therapy.

* Daily doses of GCS (in terms of prednisolone) when taken orally are divided into low (less than 7.5mg), medium (7.5–30 mg), high (30–100 mg), very high (more than 100 mg) Pulse therapy (more than 250 mg).

* In most cases GCS prescribed in the form of one morning dose, or 2/3 of the daily dose is taken in the morning and the rest is about noon. In the morning the hypothalamic-pituitary-adrenal axis is less sensitive to the inhibitory effect of exogenous GCS and therefore the risk of its suppression when administered in the 1st half of the day is less than when dividing the daily dose into 3–4 parts and taking them through equal interval of time.

* With high activity of some disease, the approximate initial dose of GCS is 1 mg/kg of wt. per day every 8 hours.

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* Cortisone :- is currently practically not used due to its lower efficacy and worse tolerance. The main area of application is replacement therapy for adrenal insufficiency with preserved liver function. (Since cortisone turns into active hydrocortisone in the liver).

7) Risk factor of adverse effect of Corticosteroids (what should we assess before administration).

- Relative contraindication of GCS :-
  1. Diabetes mellitus (especially dangerous fluorinated GA)
  2. Mental illness, epilepsy
  3. Peptic ulcer and duodenal ulcer
  4. severe osteoporosis
  5. Severe arterial hypertension
  6. severe heart failure
  7. obesity
- In the presence of these factor the appointment of GCS is not excluded, but more careful monitoring of the pt's condition and correction of existing problem are required.

Doses :- When taking higher doses (more than 30mg/day) functional inhibition of the adrenal cortex occurs after 1-2 weeks and its atrophy further develops. Full restoration of the function of adrenal cortex in the course of 2-3 weeks occurs in

G-12 mo
- Equation :-
40mg/day
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6-12 months.

- Duration :- for upto 10 days course (dose not more than 40 mg/day of prednisolone) or when taking less than 8 weeks of no more than 20 mg of prednisolone. there is no danger of inhibition of HHF and rapid cessation of treatment in these cases. is not accompanied by the development of withdrawal syndrome.

- Time of Administration - It is more dangerous to give 5mg of prednisolone in the evening than 20 mg in the morning.

- Type of Drug :- fluorinated GCS (triamcinolone, dexamethasone, betamethasone) inhibit HHF.

- Dose reduction Tactics :-
In order to avoid withdrawal syndrome like (weakness, malaise, fatigue, loss of appetite, myalgia fever. (mild cases) in severe cases like especially under high stresses a classic addison crisis may develop :- collapse, vomiting, convulsion. Patients quickly die from acute cardiovascular failure.) we have to use the dose gradually in these cases.

- Moderate and high dose - 5-10 mg/week.
- less than 20mg - 1.25 - 2.5mg/week.
- less than 10mg - 1.25 mg/week and slower.

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8) Adverse Effect of Glucocorticosteroids.
- Increased appetite, Cushing Syndrome (central obesity, moon face, buffalo hump)
- Increased Susceptibility to infection.
- Growth inhibition (children).
- Osteoporosis, aseptic osteonecrosis.
- Myopathy.
- Atrophy of the skin, striae, wound healing decline
- Edema, arterial hypertension.
- Hypokalemia, hypokalemia alkelosis.
- Hyperlipidemia, hypercholesterolemia (atherosclerosis) hypertaglyceridemia.
- Diabetes.
- Pancreatitis, Stomach and duodenum ulcers.
- Mental disorders.
- Cataract, glaucoma
- Secondary amenorrhea, impotence, hirsutism.
- GCs cause changes in CBC - neutrophilic leukocytosis, ↓se in content of lymphocytes, monocytes, basophils and eosinophils, stimulating the formation of RBC and platelets.

5) Treatment with Glucocorticosteroids: - Short term, long term, alternating, intermittent treatment.

⇒ Short term administration cause: weakness, hyperglycemia, fluid retention

Intermittent GCs therapy is ... treatment for acute exacer... disease, while minimizing th... use of GCs. Intermittent ... for certain acute conditions ... or inflammation, to q...

Mood cha...
- Cortisone
- Short term
acute ...
- Treatment

⇒ Long term
- Suppression
- Infection
- Cataract
osteoporosis
- Growth

* Long term
disease ...
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⇒ Interm...

Intermittent use treatment for acute exacerbation of chronic condition, such as asthma or autoimmune disease, while minimizing the risk of side effects associated with long term use of GCs. Intermittent GCs therapy can also be used for certain acute conditions such as severe allergic rxn or inflammation, to quick reduce inflammation & symptoms.

GCs therapy is to provide a rapid & effective anti-inflammatory & immunosuppressive

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Mood changes, insomnia

- Cortisone and Cortisol are short acting
- Short term therapy often prescribed for pt. with acute bronchitis associated with asthma or COPD.
- Treatment is for less than 30 days

⇒ Long term administration causes :-

- Suppression of the HPA axis. (most serious)
- Infection, cardiovascular disorder
- Cataract, glaucoma, obesity, hyperlipidemia osteoporosis, peptic ulcer disease, Muscle atrophy.
- Growth retardation in childhood, hypertension

* Long term use mainly in chronic inflammatory disease such as Rheumatoid arthritis, IBD urticaria, atopic eczema, COPD, lupus.
* Long term duration is more than 30 days.

⇒ Alternate treatment with GCs :-

- To avoid suppression of the hypothalamus-pituitary-adrenal axis, it is essential not to use the long acting corticosteroids betamethasone and dexamethasone.
- ↓ se adverse effect of the treatment and also a ↓ se in serum levels of autoantibodies.

⇒ Intermittent treatment with GCs :- Enhance

The aim of pulse therapy is to achieve a therapeutic effect while minimizing the risk of side effect associated with long term continuous medication use.

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muscle repair without causing muscle atrophy. GCS such as prednisolone are prescribed for chronic muscle condition such as Duchenne muscular dystrophy. Also the intermittent dose ↓ the risk of muscle atrophy.

Q6 Pulse therapy (Indication, principle of GCS administration, complication).

- The term pulse therapy refers to discontinuous IV infusion of very high doses of drugs over a short time eg Methylprednisolone, dexamethasone,
- It is usually 10 to 20 mg per kg of body weight for methylprednisolone (250-1000 mg) and 2 to 5 mg per kg of body wt (50-200 mg) for dexamethasone

Indication of pulse therapy :-

- Steroid resistant and steroid dependent nephrotic syndrome.
- Rapidly progressive glomerulonephritis
- Systemic vasculitis
- SLE
- Acute renal allograft rejection
- Juvenile Rheumatoid arthritis
- Juvenile Dermatomyositis
- Pemphigus
- Optic neuritis.

Complicati
- Hyperten
- Arrhythm
- Hypokala
- Psychosis
- Infection

Princip
- only use
- Avoid us
- Use sh
- Keep the

Antihyp

Q1. Normal

Category
optimal
Normal
High norm
Grade 1
Grade 2
Grade 3
Isolated
Hyperte

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Complication of Pulse therapy

- Hypertension
- Arrhythmias
- Hypokalemia
- Psychosis
- Infections

Principle :-

- only use drugs if they are essential.
- Avoid use of long acting drugs.
- Use short acting and intermediate acting drugs
- Keep treatment as short as possible.

Antihypertensive Drugs

Q1. Normal and target blood pressure levels.

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 HTN	140-159	and/or	90-99
Grade 2 HTN	160-179	and/or	100-109
Grade 3 HTN	≥180	and/or	≥110
Isolated Systolic Hypertension	≥140	and	<90.

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Q2) Characteristics of the Stage, degree and risk of hypertension.

" High normal SBP - 130-139
DBP - 85-89

- Stage 1 (uncomplicated)
  No other risk factor - Low risk
  1 or 2 risk factor - low risk
  ≥ 3 risk factor - low to moderate risk factor.

- Stage 2 (asymptomatic Disease)
  → High normal
  SBP - 130-139
  DBP 85-89

⇒ CKD Grade 3 or diabetes mellitus without organ damage → the risk to high risk

- Grade 1 (140-159 / 90-99) - High risk
- Grade 2 (160-179 / 100-109) - High risk
- Grade 3 (≥180 / ≥110) - High to very high risk.

Stage 3 (Established disease)
established CVD, CKD grade ≥4 or DM with Organ Damage.
High normal - Very high risk.
Grade 1 - Very high risk.
Grade 2 - Very high risk.
Grade 3 - Very high risk.

Grade 1 (40-15
(90-
Low risk
Moderate risk
Moderate to h
risk

Q3) Prin
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Grade 1 (140-159) (90-99)	Grade 2 160-179 / 100-109	Grade 3 ≥180 / ≥110
Low risk	Moderate risk	High risk
Moderate risk	Added to high risk	High risk
Moderate to high risk	High risk.	High risk.

(Q3) Principle of drug antihypertensive therapy as well as non drug method of treatment. Characteristics of first line antihypertensive drugs. Features of the action. Indication and C/I for each group. Side effects.

⇒ The goal of treatment is to reduce the risk of CVD and complications

→ Life style changes

→ It is recommended that the 1st objective of treatment should be to lower BP to < 140/90 mmHg in all patient.

→ The decrease of BP should be gradual

→ It is important to achieve and maintain the target BP with the minimum necessary drugs.

a) Rational choice of drug

b) Adequate combination of antihypertensive drug (ADHD)

c) Rational dosage of ADHD

- Using long term CAHD (24 hours or more - Stable hypotensive effect, 24 hr protection of target organs and increasing the patients adherence to treatment
- Treatment of HTN in acute situation (Stroke, acute heart failure, arterial embolism, acute pan hypercatecholaminemia) - impact to the main etio-pathogenetic cause

CAHD Should reduce :-
- Total peripheral vascular resistance
- The minute volume of blood flow.
- The volume of circulating blood.
- Prevent remodeling of the vascular wall and the development of left ventricular myocardial hypertrophy

Properties of the ideal CAHD
- Effective reduction of the BP to the target level
- High efficiency when used as a monotherapy.
- To give rational combinations with other CAHD
- To be prescribed once per day to maintain high adherence of the patients to treatment (To have an effective duration of action over 24 hours)
- To give a direct dose dependent effect
- To have an optimal tolerability profile

Life style intervention
=> 9t is recommen
- Salt restriction
- To restrict alcoh
unit per week for
week for women
- Increased consump
fish nuts and
low consumption
low fat dairy
- Body weight co
Obesity (BMI
>102 cm in men
aiming a healthy
waist circumfer
cm in women
- Regular aerobic
moderate dynami
- Smoking cess
to smoking

* 1st line a
CACEI

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Life style intervention for patients with HTN

=> It is recommended -

- Salt restriction to <5 gm per day
- To restrict alcohol consumption to less than 14 unit per week for men and less than 8 unit per week for women.
- Increased consumption of vegetable, fresh fruits, fish nuts and unsaturated fatty acid (olive oil) low consumption of red meat and consumption of low fat dairy products
- Body weight control is indicated to avoid obesity (BMI >30 kg/m2 or waist circumference >102 cm in men and >88 cm in women) as is aiming a healthy BMI (about 20-25 kg/m^2) and waist circumference value (<94 cm in men and <80 cm in women)
- Regular aerobic exercises (eg at least 30 min of moderate dynamic exercise on 5-7 days per week)
- Smoking cessation, supportive care, and referral to smoking cessation programs.

* 1st line antihypertensive Drugs

ACEI	ARB
- Captopril	→ Valsartan
Ramipril	- Losartan
Enalapril	- Telmisartan
Quinapril.	- Irbesartan

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Renin inhibitor
- Aliskiren

Beta Blocker
- Metoprolol
- Atenolol
- Propranolol
- Timolol
- Alprenolol

Diuretics
- Hydrochlorothiazide
- Indapamide
- Clopamide
- Chlorthalidone

Calcium channel blocker

Dihydropyridine	Verapamil	Diltiazem
Nefedipine		
Nitrendipine	Verapamil	Diltiazem
Isradipine	Anipamil	Clentiazem
Nicardipine	Devapamil	
Amlodipine	Tiapamil	
Felodipine	Gallopamil	

Factor that determine the choice of the drug
- Presence of risk factor
- Presence of asymptomatic organ damage
- Presence of coronary heart disease, cerebrovascular disease and renal disease
- Socio-economic factor including the cost of treatment

* Indications

Diuretics - Heart failure
- Renal insufficiency (loop diuretics)
- Post MI (anti aldosterone)

CCB -

CACEI →

ARB →
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→ P
→
→ A

B Blocker -

* Contraind

Drugs

Diuretics
(Thiazides/thia
like agents
lidone and
indapamide

Beta Blocke

CCB - Elderly pts
- Angina pectoris
- Peripheral vascular disease
- Pregnancy.

ACE I → Heart failure
- LV dysfunction
- Post myocardial infarction
- Non diabetic nephropathy

ARB → Typ 2 diabetic nephropathy
→ Typ 2 diabetic micro albuminuria.
→ Proteinuria
→ LVH
→ ACE-I cough or intolerance

β Blocker - Angina pectoris.
Post MI
HF
Tachyarrhythmias

* Contraindication of the use of AHD

Drugs	Contraindication	
	Compelling	Possible
Diuretics (Thiazides / thiazide like eg chlorthalidone and Indapamide	Gout	Metabolic Syndrome glucose intolerance Pregnancy, hypercalcemia hypokalaemia.
Beta Blocker	Asthma, any high grade sinoatrial or atrioventricular block, bradycardia (HR < 60 bPm.)	Metabolic Syndrome glucose intolerance athletes and physically active patients

Drugs	Contraindication: Compelling	Contraindication: Possible
Calcium Antagonists. (dihydropyridines)		Tachyarrhythmia, heart failure (class III or IV), pre existing severe leg oedema
CCB (verapamil diltiazem)	Any high grade Sinoatrial or atrioventricular block severe LV dysfunction (LV ejection fraction <40%) Bradycardia (heart rate <60 BPM)	Constipation.
ACE I	Pregnancy Previous angioneurotic oedema, hyperkalaemia Bilateral renal artery Stenosis	Women of child bearing potential without reliable Contraception
ARB's	Pregnancy hyperkalaemia (>5.5 mmol/L) bilateral renal artery Stenosis	Women of child bearing potential without reliable Contraception

Major adverse

- ACE I - patients with
- ARB → like
- CCBS (dihydro rash, gra
- Diuretics (thia muscle cramp hypercholesterol Hypokalemia, hyponatraemia
- Beta Blocker - Bradycardia, impotence, nightmares, d
- alpha blocker Dizziness, h
- Central alpha Bradycardia sexual dysf
- Peripheral - sedation,

(Q4) ACE in

Indication

=) That high

→ They work

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Major adverse Effects

- ACE I - Dry cough, renal dysfunction in patients with impaired renal function
- ARB → like in hepatic Enzymes levels
- CCBS (Dihydropyridines) - Headache, palpitation rash, gravitational oedema.
- Diuretics (thiazide like) - Dry mouth, thirst, muscle Cramps, impotence, hyperglycemia, hypercholesterolaemia, abnormality in electolytes (hypokalemia, hypomagnesaemia, hypercalcaemia, hyponatraemia), pancreatitis.

- Beta Blocker - High degree atrioventricular block bradycardia, heart failure, Raynaud phenomenon, impotence, fatigue, sleep disturbance including nightmares, depression, alteration of lipid profiles.

- Alpha blocker - Orthostatic hypotension, Syncope, Dizziness, headache, drowsiness
- Central alpha agonist - Orthostatic hypotension Bradycardia, drowsiness, dry mouth, galactorrhoea, sexual dysfunction
- Peripheral alpha agonist (Reserpine) - Depression, sedation, nasal Stuffiness.

(Q4) ACE inhibitor - Mechanism of action Indication and Contraindication.

=) Treat high BP and heart failure

→ They work by causing relaxation of blood

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vessels as well as ↓ in blood volume which leads to lower B.P and decrease oxygen demand from the heart.

→ ACEI inhibit the activity of angiotensin converting enzymes, an important component of the renin angiotensin system which converts angiotensin I to angiotensin II and hydrolyses bradykinin.

→ Therefore ACEI use the formation of angiotensin II, a vasoconstrictor, and ↑se the level of bradykinin, a peptide vasodilator. This combination is synergistic in lowering BP.

ACEI Effects (MOA)

- On ↑se in plasma renin level
- ↓ decrease in the concentration of angiotensin II
- ↓se of aldosterone release
- Also they prevent the destruction of bradykinin.
- The vasopressor antidiuretic and antinatriuretic action of angiotensin II disappears.
- The vasodilating and natriuretic action of bradykinin increases
- Prostaglandins of the vascular wall are activated which have an independent vasodilating effect

- Improve
- system
- Metabolic
- Organopro
- Anti prolif
- Anti unf
- Anti coagu

* According
enzyme
following

Zofenopril
Lisinopril

Contraindi

- Pregnancy
teratogenic
- Lactation
- Angio
- Idyperk
- Bilateral
Stenosis

Indication

- Improve the function of the cardiovascular system
- Metabolic
- Organoprotective
- Antiproliferative
- Anti inflammatory
- Anticoagulant effects.

Side effect of ACEI :-
- arterial hypotension
- Tachycardia.
- acute renal failure
- Dry cough due to bradykinin
- bronchitis, dyspnea
- GI system → nausea, pain in epigastric region, vomiting, hepatitis
- urticaria, pruritis, photosensitivity
- anxiety, ↓ libido, leukopenia

* According to the degree of affinity for tissue isoenzymes, ACE inhibitor are arranged in the following order

Zofenopril > Quinapril > Ramipril > Perindopril > Lisinopril > Enalapril > Fosinopril > Captopril

Contraindication

- Pregnancy - ACEI have a fatotoxic and teratogenic effects.
- Lactation
- Angioedema in anamnesis
- Hyperkalemia
- Bilateral Stenosis of the renal arteries, Stenosis of the artery of a single kidney

Indication

Heart failure
LV dysfunction
Post MI
Non diabetic nephropathy.

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Q5) cAT receptor blocker - Indication contraindication side effect.

- cAT1 receptor blocker weaken the action of angiotensin II, regardless of how it was formed
- They irreversibly block the cAT1 receptors of the cardiovascular system, kidney and to a lesser extent, the adrenal glands.
- The spectrum of indication is similar to cACE inhibitors
- Traditionally they are prescribed as reserve drugs for intolerance to cACE inhibitors.
- They do not cause dry cough, they are well tolerated (withdrawal frequency is no more than 1-2%)
- Higher cost

Contraindication

- Pregnancy
- Hyperkalaemia (potassium > 5.5 mmol/L)
- Bilateral stenosis of the renal arteries, stenosis of the artery of a single kidney

Side effects

- Cardiovascular System - Orthostatic reaction, palpitations, arterial hypotension.
- GI Tract - Diarrhea, dyspepsia, nausea increased bilirubin level
- CNS - Dizziness, headache

- Given to urin
of creatinin
- Hematopoie
and hema
- Allergic rea
serum sick
- Electrolyt

Q6) Alpha b
Side effe

=>

Non-Selecti

Irreversible

Selective α1

- Doxazosin
drug for
- Their appoin
and in su
prostatic h
mellitus,
COPD.

=> α adrenerg
condition

- Genito urinary System - An increase in the level of creatinine and urea nitrogen.
- Hematopoiesis - neutropenia, a ↓se in hemoglobin and hematocrit.
- Allergic reactions - Angio edema, rash, itching serum sickness, vasculitis
- Electrolyte imbalance - Hyperkalemia.

Q6) Alpha blocker. Indication contraindication. Side effects.

⇒ (lassification of α blocker

- Non-selective
  - Irreversible
  - Reversible
    - → Ergot alkaloids
    - → Imidazolines
    - → Miscellaneous
- Selective
  - α1 selective
  - α2 selective

Selective α1 - blocker

- Doxazosin and terazosin are used as second line drug for hypertension.
- Their appointment is preferably in heavy smoker and in such concomitant disease as benign prostatic hyperplasia, erectile dysfunction, diabetes mellitus, atherogenic dyslipidemia, bronchial asthma, COPD.

→ α adrenergic blocker are C/I in hypotensive condition (Systolic BP < 80 mm Hg). a tendency

doxazosin, porazosin & terazosin

Ind
(1) Hypertension
(2) Benign prostatic hyperplasia
(3) Raynaud disease

Contra
- Allergy
- Hypotension
- Pulmonary disease
- ~~Pregnancy & breastfeeding~~

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to orthostatic reactions, severe atherosclerosis of the coronary and cerebral vessels, tachycardia, aortic stenosis, patent ductus arteriosus, heart defects with reduced blood supply to the left ventricle, pregnancy, breast-feeding, children under 12 years of age. Doxazosin is not prescribed for liver disease.

✗ CNS of central action -
α_2 - adrenergic receptors agonists I 1 imidazoline receptor agonists.

→ Imidazoline I_1 receptors of the ventrolateral nuclei of the medulla oblongata and α_2 adrenergic receptors of the nucleus of the solitary tract participate in the regulation of the central sympathetic tone and activity of vagus nerve.

→ When these receptors are activated, the pressor function of the vasomotor centre is weakened and the tone of the vagus nerve increases

→ Central α_2 agonists clonidine, guanfacine and methyldopa, by activating presynaptic α_2 adrenergic receptors, inhibit the release of nor adrenaline, dopamine, acetylcholine, glutamic acid.

- They reduce centre and increase the

Clonidine -
- It has ant and hypothe
- Clonidine d vascular resi
→ It reduces
→ Inhibit vaso
→ Dilate the Coronary ves
→ Prevent LV
→ normalizes
→ Clonidine a tensive crisi

Side Effect
Sedation, conjunctiva impotence

Methyldo
- In young methyl dop without output

- They reduce the excitability of the vasomotor centre and the central sympathetic tone, increase the tone of the vagus nerve

Clonidine :- It is an imidazoline derivative
- It has antihypertensive, sedative, analgesic and hypothermic effects.
- Clonidine dilates peripheral arteries and reduces vascular resistance
→ It reduces heart rate and minute blood volume
→ Inhibit renin secretion and RAS function
→ Dilate the vessels of the kidney, brain and coronary vessels.
→ Prevent LVH.
→ normalizes sleep
→ Clonidine can be used for treatment of hypertensive crisis (under the tongue per os intravenously)

Side Effect of Clonidine :-
Sedation, Dry mouth, nasal mucosa and conjunctiva, nausea, vomiting, constipation, impotence, Depression, Bradycardia.

Methyldopa
- In young people with uncomplicated hypertension methyldopa reduces peripheral vascular resistance without a significant effect on cardiac output and heart rate.

In elderly patients, It causes bradycardia, weakens the contraction of heart and reduces the cardiac output.

- Methyldopa dilates arteries more than veins, therefore lowering blood pressure without pronounced orthostatic fluctuation.

- It causes regression of left ventricular hypertrophy, improves cerebral and renal blood flow and has a sedative effect.

- With long term treatment with methyldopa, addiction occurs due to impaired renal excretion of sodium and water ions.

- It is taken orally for arterial hypertension as a second line agent.

- Side effects:- Depression, strong sedative effects, parkinsonism, bradycardia, autoimmune hemolytic anemia, hepatotoxic, disorder with cholestasis and Jaundice

- Less commonly other side effects occur are leukopenia, thrombocytopenia, aplastic anemia, SLE, myocarditis, pancreatitis.

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I1 imidazoline receptor agonists

- selective I1 receptor agonists moxonidine and rilmenidine activate I1 receptor 40-70 times stronger than α2- adrenergic receptors.
- In the blood they reduce the activity of renin reduce the content of norepinephrine, adrenaline and to a lesser extent angiotensin II aldosterone natriuretic peptides.
- They inhibit the function of osteoclasts and slow down bone resorption, improve mood and reduce anxiety.

⇒ Side effect of I1 receptor agonists are due to non selective activation of α2 adrenergic receptor asthenia, drowsiness, dry mouth, dyspeptic disorders.

* I1 receptor agonists are C/I in sinus node weakness, bradycardia (< 50 per min), atrioventricular block II, III degree, severe arrhythmia, CHF, unstable angina, hepatic and renal insufficiency (creatinine clearance < 30 ml/min)

⇒ This drug are not prescribed for pregnant women people under the age of 18, on an outpatient basis for people whose profession requires high mental and physical activity. At the time of treatment stop breastfeeding.

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Q7) Hypertensive crises. Treatment of uncomplicated hypertensive crises (Hypertensive urgency).

- Urgency Hypertensive → Blood pressure is 180/120 mm Hg or greater. There is no signs of organ damage.

Symptoms - Anxiety, Blurred vision, chest pain, Confusion, Seizures, Shortness of breath.

Treatment → Treat in outpatient facility with oral antihypertensive drug.

→ Slow lowering of BP of no more than 25% within the first 24 hours.

⇒ Captopril, clonidine, and labetalol have been used.

→ Sublingual or oral nifedipine is no longer recommended due to its property to cause severe hypotension and organ ischemia.

Q8) Complicated hypertensive crises. (Hypertensive emergency) Treatment.

- Hypertensive emergencies are defined as large elevation of SBP or DBP (>180 mmHg or >120 mm Hg respectively) associated with impending or progressive organ damage and require immediate

controlled
or limit
infarction
coronary
acute LV
pheochromo
Subarachnoid

Treatment
Treatment
a < 25
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Prompt and
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aortic d
reduction
time to
110 mm Hg

* Admission
- Continuous
of urine
→ Labetalol
Nitroprus
individua

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Date

controlled blood pressure reduction to prevent or limit organ damage such as cerebral infarction, hypertensive encephalopathy, acute coronary syndrome, acute pulmonary oedema (acute LV failure, aortic dissection, renal failure, pheochromocytoma hypertensive emergency, eclampsia, intracranial haemorrhage.

Treatment :-

- Treatment should be started immediately, aiming at a < 25% BP reduction during the 1st two hours with the subsequent achievement of target BP within a few hours (no more than 24-48 hr) from the start of therapy.

- Prompt and aggressive BP reduction is required in acute pulmonary oedema (acute LV failure) or aortic dissection (aiming at a < 25% BP reduction during the 1st 5-10 min the optimal time to reach the target level of SBP 100-110 mm Hg is no more than 20 min.

* Admission to the ICU.

- Continuous cardiac monitoring, frequent measurement of urine output, neurologic assessment.

- Labetalol, Esmolol, Nitroglycerin, Sodium Nitroprusside but their use are limited to individual with myocardial ischemia, and acute

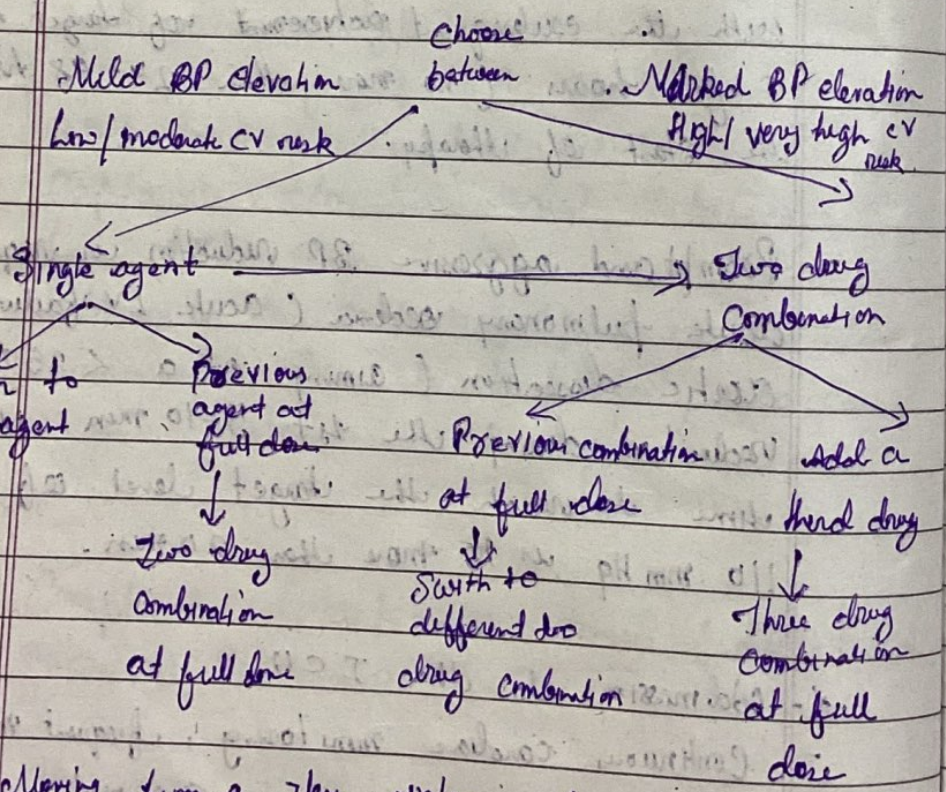
pulmonary edema or aortic dissection.

→ Clevidipine (IIIrd generation) ⇒ 1st agent for hypertensive emergency. (CCB ⇒ Dihydropyridine)

→ Trimethaphan, phentolamine, Catecholamine

→ IV Esmolol include a loading dose of 20mg followed by 20 to 80 mg doses repeated every 10 minutes until desired BP is attained

Q9) Combination therapy for hypertension: Rational possible, Irrational Combination:-



→ Moving from a less intensive to a more intensive therapeutic strategy should be done until BP target is not achieved.

Possible Co

→ Preferred
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→ Useful comb

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Beta blo
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other anti

→ CNot reco
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* Verapamil
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* only Dih
Should nor

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Possible combination of antihypertensive drugs

→ Preferred combination are :- Thiazide diuretic + ACEI
Thiazide diuretics + Calcium antagonist
Thiazide diuretics + ARB.
ACEI + Calcium antagonist
Calcium antagonist + ARB.

→ Useful combination with some limitation :- Beta blocker + Thiazide diuretics

→ Possible but less well tested combination :-
Beta blocker + ARB
Beta blocker + Calcium antagonist
Beta blocker + other antihypertensive
ACEI + other antihypertensive
other antihypertensive + calcium antagonist
" + ACEI
" + ARB
" + Thiazide diuretics.

→ Not recommended Combination :-
ACEI + ARB.

* Verapamil and diltiazem are sometimes used with a beta blocker to improve ventricular rate control in permanent atrial fibrillation.
* only Dihydropyridine calcium antagonists should normally be combined with β Blocker.

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* Rational combination provide greater antihypertensive power than ~~than~~ the use of high dose of monotherapy.

X Irrational combination can lead to reduction in quality of drug therapy, increased risk of side effect, drug resistance
eg - Enalapril + Losartan combining two drugs affecting the same pathway is irrational

Q10) Preferred choice of antihypertensive drugs depending on the clinical situation.

- Primary prevention → Thiazide diuretics, ACEI or ARB or combo

	1st line	2nd therapy
- DM →	ACEI or ARB →	Thiazide → CCB or β Blocker
- Chronic kidney Dx →	ACEI or ARB.	
- Coronary artery Dx (acute or chronic) →	β Blocker and ACEI or ARB	Thiazide for BP control; CCB for Ischemia control
- Prior Ischemic Stroke →	ACEI or ARB and thiazide	

Left vent

ACEI
thiazide
and β-

Expe

Q1) Classific

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1) Direct
→ Mucolytic
(Viscosi
* Thiol
* Proteol
→ Mukog

2) Indirect
- Mucoreg
- Surfac
- Gastro-
(expect
- Broncho
phenat
* Drugs
for other

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Left ventricular Dysfunction

↓

ACEI or ARB and thiazide (or loop) diuretics and β-Blocker.

→ Aldosterone antagonist if severe HF

→ Hydralazine and isosorbide dinitrate if Black.

Expectorants

Q1) Classification of expectorants (Mucokenetics)

*) Mucolytics classification.

1) Direct acting agents.

→ Mucolytics, affecting the rheological properties (viscosity and elasticity) of mucus

* Thiolytics

* Proteolytic Enzymes

→ Mukogidrant.

2) Indirect acting agents.

- Mucoregulator
- Surfactive and thinning secret.
- Gastro-pulmonary reflex stimulating drugs (expectorant, mucokinetics)
- Bronchorriks: Pinenes, terpenes, methanes, phenol derivatives

* Drugs that affect bronchial secretion, but used for other indication (Ipratropide)

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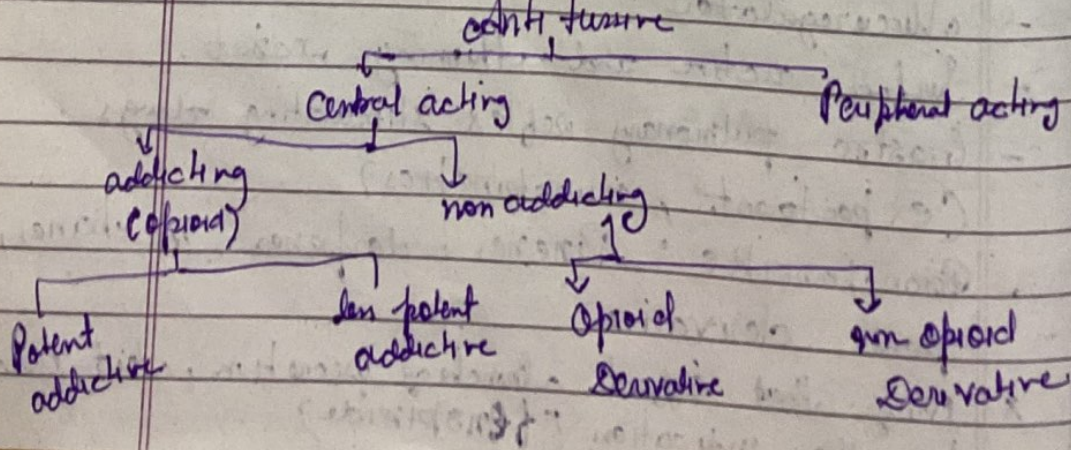
Q2 Characteristics of expectorants of plant origin. Mechanism of action. Indication and contraindications for appointment. Side effects

Q1 a) Antitussive, Classification. (Suppress cough)

1) Central action drugs
- Central action narcotic antitussive drug – Codeine ethylmorphine, dextromethorphan.
- Non narcotic antitussive drugs of central action oxeladine, butamirate (Sinecode), glaucin (glauvent), pentoxiverine, oxedine, folcodine.

2) Non narcotic antitussive drugs of peripheral action – prenoxdiazine (libexin), levodropizin, benproapirin, bitiodine

3) Combined –:
- With antitussive and expectorant effects (Stoptussin)
- With antitussive, bronchodilator and antimicrobial effects (Bronchalitin)



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Expectorants

- Secretion enhancers
  - Sodium / Potassium citrate
  - Potassium iodide
  - Guaiphonesin
- Mucolytics
  - Bromhexine
  - Ambroxol
  - acetyl cysteine
  - Carbocisteine

(Imp) Based on MOA Expectorants are categorised into 2 types :-

1) Sedative expectorants
2) Stimulant expectorants

They thin and loosen the mucus in the respiratory tract.

Q2 Any Expectorant of plant origin are :-

- Licorice root, shoots oregano
- Marshmallow root, leaves of coltsfoot
- Ipekakuana root, eucalyptus, pine buds
- Senega, sundew, thyme, Mullein (mucolytic & anti-inflammatory property)
- Rhizomes with elecampane and cyanosis root
- Anise and fennel fruit. > ginger, peppermint

Characteristics :-

- They promote the secretion and clearance of mucus from the respiratory tract
- They often used to treat condition such as cough, bronchitis, other respiratory tract infection.
- → They are generally safe and well tolerated.

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Mechanism of action

- The exact mechanism of action of expectorants of plant origin is not completely understood:
- They work by increasing the volume and reducing the viscosity of respiratory tract secretions, thereby making it easier for the body to expel them.

Indications :-

- Treat the condition associated with excessive mucus production in the respiratory tract, including acute and chronic bronchitis, asthma, and other respiratory tract infections.

Contraindication :-

-> If allergic to that plant
-> Liquice is C/I in hypertension because it increase in BP.
-> It should not be used in individuals who are taking medication that suppress cough or in individual who have chronic cough due to smoking or other respiratory irritants

Negative
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- That vac
- May cause
- Can use

Side effe
- Nausea
- In rare
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Q3) Expectoran
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Negative Effect of expectorant herbal drugs:-

- The lack of effectiveness of small doses.
- Short reaction
- May cause nausea, vomiting.
- Can use in the volume of bronchial secretions

Side effects :-

- Nause, vomiting, Stomach upset
- In rare cases these product may also cause allergic reaction such as skin rash, hives, or difficulty breathing

Q3) Expectorants acting on the bronchial mucosa. Features of the action. Indication and contraindication for appointment. Side effects.

→ Help to stimulate the bronchial glands and increase the production and clearance of mucus from the respiratory tract.

→ Example of these type of expectorants include ammonium chloride, potassium iodide and senega.

Characteristics

- These expectorant work by irritating the bronchial mucosa, which stimulates the production of mucus.
- They also have a direct effect on the cilia of the respiratory tract, which helps to

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more mucus up and out of the airways.
- They are often used to treat condition such as acute and chronic bronchitis, asthma and other respiratory tract infection

Indication :-
- Expectorants that act on the bronchial mucosa are indicated for the treatment of conditions associated with excessive mucus production in the respiratory tract, including acute and chronic bronchitis, asthma and other respiratory tract infections.
- They are also sometimes used to help in removing inhaled particles or to improve the effectiveness of nebulized medication.

Contraindication :-
- Allergy.
- Individual who have a chronic cough due to smoking or other respiratory irritants.
- Individual with certain medical conditions such as liver or kidney disease, heart disease, or high blood pressure.

Side Effects
→ Stomach upset
• Diarrhea.
→ ↑ in heart rate
individuals
→ May cause allergic
side effects such
breathing.

(Q4) Mucolytics... Mu
Side effects.
- Mucolytics are
break down and
easier to expe
- They work by
structure of
viscosity and
eg - Acetylc
Carbocisteine.

Mechanism of
Mucolytics wo
chemical bonds
reducing its
easier to co
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Side Effects

→ Stomach upset, nausea, vomiting.
• Diarrhea.
→ ↑ in heart rate or blood pressure in some individuals.
→ May cause allergic reactions or other serious side effects such as seizures or difficulty breathing.

(Q4) Mucolytics. MOA, Indication and C/I Side effects.

- Mucolytics are substance that helps to break down and liquefy mucus, making it easier to expel from the respiratory tract.
- They work by breaking down the molecular structure of the mucus, which reduces its viscosity and makes it less sticky.
eg - Acetylcysteine, Bromhexine and Carbocisteine.

Mechanism of Action

Mucolytics work by breaking down the chemical bonds that hold mucus together, reducing its viscosity and making it easier to cough up and clear from the airways. This allows for easier breathing and improved lung function.

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Indications :-

- Mucolytics are indicated for the treatment of conditions associated with excessive mucus production in the respiratory tract including acute and chronic bronchitis, cystic fibrosis, and other respiratory tract infections.

- They are also sometimes used to improve the effectiveness of other respiratory medications, such as bronchodilators or corticosteroids.

Contraindications :-

- Allergic to ingredients in mucolytics.
- Should not be used in individuals who have chronic cough due to smoking or other respiratory irritants.
- Contraindicated in individuals with certain medical conditions, such as asthma, peptic ulcer disease or liver disease.

Side Effects

- Stomach upset, nausea, vomiting, diarrhea.
- ↑ heart rate or blood pressure in some individuals, in rare cases they may cause allergy or other serious side effects such as bronchospasm or difficulty breathing.

Bronchodilato

Q 1) Classification of

β_2 adrenergic ag

1) Short acting β_2
- Salbutamol, terbu
  ↳ Partial

2) Long acting β_2
- With a rapid on
  olodaterol, u
- With delay acti

Muscarinic anta
- Short acting (ip
- long acting (tio
  bromide, glyco

Methylxanthine
- Theophylline.
- Fast acting
- Sustained releas
  24 hours acti

Q2) Selective β_2
- Of the acti
  appointment.

⇒ Selective β_2
as albuterol

Bronchodilators

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Q 1) Classification of bronchodilator.

β_2 adrenergic agonists classification.

1) Short acting β_2 adrenergic receptor agonists
- Salbutamol, terbutaline, fenoterol
  ↳ Partial ↳ complete.

2) Long acting β_2 adrenergic receptor agonists
- With a rapid onset of action (formoterol, ↳ complete.
  olodaterol, undacaterol)
- With delay action (: salmeterol).
  ↳ partial.

Muscarinic antagonist classification
- Short acting (ipratropium bromide)
- long acting (tiotropium bromide, umeclidinium bromide, glycopyrronium bromide)

Methylxanthine classifications
- Theophylline. - Two form of theophylline are used
- Fast acting drugs
- Sustained release theophylline formulation (12 and 24 hours action)

Q2) Selective β_2 adrenergic receptor agonists. Of the action. Classification. Indication for appointment. Side effects.

⇒ Selective β_2 adrenergic receptor agonists such as albuterol or Salbutamol are a type of

Activation of β adrenergic receptor leads to relaxation of smooth muscle in the lung, and dilation & opening of the airways.

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medication commonly used to treat condition such as asthma or COPD

- These medication work by specifically targeting and stimulating the B_2 adrenergic receptors which are located primarily on the bronchioles of the lungs.
- When these medication binds to the B_2 adrenergic receptors, they trigger a cascade of intracellular events that ultimately lead to the relaxation of the smooth muscles in the bronchioles. This relaxation allows the airways to open up and air to flow more easily, making breathing easier for individuals with respiratory conditions.
- The MOA is based on binding B_2 adrenergic receptor and its activation the activity of adenylate cyclase increases the accumulation of cAMP in the cell activation of myosin light chain kinase ↓ use in the intracellular concentration of calcium

Pharmacological Effects :-

- Bronchi - Bronchodilation, increased mucociliary clearance.
- Heart - Positive chronotropic and dromotropic effects, improved conductivity through the atrioventricular node, proarrhythmic effect, ↑ed myocardial oxygen demand.

- Vessels -
- Mast cell -
- Skeletal mus
- Liver - G
- adipose tis
- Myometriu

Indication

- for relief
agonists).
- Bronchial
B_2 adrenc

emphysema

Contraind

- Idio syn
Contraind
- Relative
- Coronary a
acute M
- Tachyarrh
- Thyrotx

Side effe

The card
Obstructive
QT interv
oxygen

- Vessels - Vasodilation.
- Mast cell - Membrane Stabilising action.
- Skeletal muscles - Increased Contractility
- Liver - Enhanced glycogenolysis
- Adipose tissue - Enhanced lipolysis
- Myometrium - Relaxation.

Indication of B_2 adrenergic agonists :-

- For relief of bronchospasm (Short acting B_2 agonists).
- Bronchial asthma and COPD (long acting B_2 adrenergic receptor agonists).

emphysema

Contraindication :-

- Idiosyncrasy is considered as an absolute Contraindication.

Relative Contraindication :-

- Coronary artery disease (unstable angina pectoris, acute MI)
- Tachyarrhythmias and arterial HTN
- Thyrotoxicosis.

Side effects

The cardiovascular changes - Tachycardia, rhythm disturbances (extrasystole, lengthening of the QT interval), ↑sed BP, increased myocardial oxygen demand.

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Metabolic changes - Can use of glucose level and free fatty acids in the blood as well as a rise in the partial pressure of O_2 in the blood due to pulmonary vasodilation and violations of the ventilation perfusion ratio.

* To minimize the risk of side effects, patients are not advised to use short acting β_2 adrenergic receptor agonists more than 4 times a day.

(Q3) Muscarinic antagonists. MOA. Preferential indications for appointment. C/I. Side effects.

- The MOA of drugs in this group is associated with the blockade of m_1, m_2 and m_3 cholinergic receptors.
- Ipratropium, Tiotropium and Umeclidinium bromide are not completely selective.

Main pharmacological effects :- Heart - ↑ Rate force
- Bronchodilatory action.
- Anti inflammatory effects due to stabilization of mast cell membranes and inhibition of the inflammatory mediators release.
- Smooth muscle relaxation, Secretion ↓ from glands

- CNS - Q

Indication
→ for relief
→ Anti inflam
* Tiotropium
base line
- use in
Contraind
Narrow a
Hyperthy
Urinary
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- Digestive
- Cardiovas
cular dis
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occur in
- Sense o
pressure
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- Allergic
edema.

(Q4) Methyl
indicat
⇒ Methylxa
vessels
tion.

- CNS - Restlessness, amnesia

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Indication of Muscarinic Antagonists

→ for relief of bronchospasm
→ Anti inflammatory therapy for COPD.
* Tiotropium bromide is used only as a long term base line therapy.
- use in treatment of parkinson disease, nausea, motion sickness, urinary incontinence, irritable bowel syndrome.

Contraindication :-
Narrow angle glaucoma
Myasthenia gravis
Urinary obstruction
Gastric ulcer
~~Asthma~~

Side effect
- Digestive tract - Dry mouth and constipation
- Cardiovascular System - Tachycardia, Supraventricular tachycardia, and atrial fibrillation.
- Genitourinary System - urinary retention may occur in men with benign prostatic hyperplasia.
- Sense organs - can increase in intraocular pressure is noted in patients with angle closure glaucoma.
- Allergic reaction - Skin reactions, Quinke's edema.

Q4) Methyl xanthines. MOA. Pharmacological effects. Indications, Contraindication. Side effects.

⇒ Methylxanthines (theophylline) expands the blood vessels of the lungs and improves blood oxygenation.

- Improves renal blood flow and increases diuresis, increases the strength and frequency of heart contraction, lowers pressure in the pulmonary circulation.
- Inhibits platelets aggregation (inhibits platelet activation factor and PGF2 alpha) increases the resistance of erythrocytes to deformation (improves rheological properties of blood), reduces thrombus formation and normalizes microcirculation;
- Increase oxygen delivery to the myocardium, (antianginal effect) by dilating coronary arteries.

Indication :-

The drug of this group are prescribed in the following cases :-

- as base line therapy drugs for COPD and bronchial asthma.
- For the treatment of bronchoobstructive syndrom of any genesis
- with pulmonary hypertension
- with sleep apnea syndrome
- with chronic cerebrovascular insufficiency
- In combination therapy of chronic renal diseases (glomerulonephritis)

Contra

- Hypo
- Bleedi
- Pepti
- Age
- Up to
- Hemor
- Arteri
- Acute
- Severe
- Epilep
- Renal

Side

- Adverse
- Depend
- Dose
- Effect
- nausea
- Dose
- Of
- Tachy
- ventric
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Contraindication

- Hypersensitivity, including to other xanthine derivatives (Caffeine, pentoxifylline, theobromine)
- Bleeding according to vanamnesis
- Peptic ulcers and duodenal ulcers
- Age upto 3 years, for prolonged oral forms up to 12 years.
- Hemorrhagic stroke
- Arterial hypertension or hypotension
- Acute myocardial infarction
- Severe tachyarrhythmias
- Epilepsy, increased convulsive readiness
- Renal and hepatic impairment.

Side effect

Adverse effect caused by theophylline are dose dependent

- Dose 15-20 mcg/ml :- Development of side effects from the digestive tract (anorexia, nausea, vomiting, diarrhea)
- Dose 20-30 mcg/ml :- The appearance of ADR from the cardiovascular system (tachycardia, rhythm disturbances up to ventricular fibrillation)
- Dose 25-30 mcg/ml - The occurrence of reactions from the central nervous system (insomnia, hand tremor, motor and mental

agitation, convulsions).

- Dose 30-50 mcg/ml :- Possible death

Pharmacokinetic :-

- At the level of absorption - the combination with antacids reduces the absorption rate of theophylline.

- At the metabolic level - The metabolic rate increases with the simultaneous administration of drugs - inducers of microsomal oxidation in the liver and conversely decreases with the combined use of cytochrome P450 inhibitors.

- At the level of elimination - Means alkalizing urine, reduces the excretion of theophylline, acidifying - increases.

Drugs affective theophylline clearance

Increase the clearance of theophylline :-

- Barbiturates
- Carbamazepine
- Phenylbutazone
- Terbutaline
- Rifampicin

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Decrease the clearance of theophylline:-

- Cimetidine
- Allopurinol
- Erythromycin
- Tetracycline
- Some fluoroquinolones
- Ciprofloxacin
- Slow calcium blockers
- Cimetidine
- Allopurinol
- Erythromycin
- [redacted]

Pharmacodynamics

- Synergism - When theophylline is combined with β_2 adrenergic receptor agonists, glucocorticoids, cromones synergism is observed - a ↓se in inflammation and an ↑se in bronchodilatory action.
- Theophylline potentiates the action of diuretics drugs that stimulate gastric secretions; potentiate the effects of drugs that excite the CNS anticoagulants, the proarrhythmic effect of cardiac glycosides and anaesthetics.

- Antagonism - It occurs when theophylline are used together with β_2 adrenergic receptor blockers.

(Q5) The main groups of drugs for the treatment of bronchial asthma. Step treatment.

- Inhaled Corticosteroids (ICS):- used for long term control medications for asthma. They

work by reducing inflammation in the airways and improving lung function. example - fluticasone, budesonide, and beclomethasone.

- Long acting beta agonists (LABAs):- This medication work by relaxing the muscles around the airways, making it easier to breathe. They are often used in combination with ICS for better asthma control. example - Salmeterol and formoterol

- Leukotriene modifiers - These medication block the action of leukotrienes, which are chemical that cause inflammation in the airways. They are often used as an alternative to ICS in people who can not tolerate steroids. Example - montelukast and Zafirlukast

- Short acting beta agonists (SABAs):- These medications are used for quick relief for asthma symptoms, such as wheezing and shortness of breath. Example include albuterol and levalbuterol.

- Anticholinergics - These medications work by blocking the action of acetylcholine

a chemical that can cause the muscles around the airways to tighten. They are often used as an alternative to SABAS in people who can not tolerate beta agonists Example include - Ipratropium and tiotropium bromide.

- Immuno modulators - These medication modify the immune system response to prevent inflammation and narrowing of the airways. Example include - Omalizumab and Mepolizumab.

The choice of medication depends on the severity of the asthma, the frequency of symptoms and the individual's response to treatment. It's important to work closely with a healthcare provider to develop an effective treatment plan for asthma.

Guideline for Asthma (HINA 2021)

I) Relievers drugs - used to treat asthma and relieve the symptoms during an attack.

II) Maintenance drugs - These are given daily on a long term basis, to prevent further attacks of asthma.

* Previously SABA were used as relievers drugs. But now low dose ICS + formoterol combination is used as relievers

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Cardiac Glycoside

Q.1) Pharmacokinetic and Pharmacodynamics of cardiac glycosides.

Pharmakokinetic of cardiac Glycoside:-

- Cardiac glycosides are a group of medication used to treat heart failure and certain arrhythmias.
- The most commonly used cardiac glycoside is digoxin, which has a narrow therapeutic index (therapeutic close ei close to toxic dose)

* Pharmacokinetic refers to the study of how a drug is absorbed, distributed, metabolised and eliminated by the body.

- Absorption - Digoxin is absorbed slowly and incompletely from the gastrointestinal tract. The absorption is affected by factors such as the presence of food, gastric pH and gastrointestinal motility. The bioavailability of digoxin varies from 60 to 80% after oral administration.

- Distribution - Digoxin is distributed throughout the body with the highest concentration found in the heart and kidneys. The drug is highly protein bound (up to 25%) and has a large volume of distribution

- Metabolism - Digoxin is primarily metabolized by liver, where it undergoes oxidation biotransformation to form several metabolites the most important of which is the inactive compound, digoxin reduction product.

- Elimination - Digoxin is eliminated primarily by renal excretion with approximately 60% of the drug excreted unchanged in the urine. The half life of digoxin is approximately 36 to 48 hours, but can be longer in patients with renal impairment.

- Factors that can affect the pharmacokinetic of digoxin include age, renal function, hepatic function, drug interaction and electrolyte imbalances. Close monitoring of serum digoxin level is necessary to ensure the drug is within the therapeutic range and to prevent toxicity.

Pharmacodynamic of Cardiac glycoside

- Cardiac glycosides are a class of drugs that have a direct effect on the heart by inhibiting the Na^+/K^+ ATPase pump, leading to an increase in intracellular calcium concentration and subsequent increase in myocardial contractility. The most commonly used cardiac glycoside is digoxin.

Q2) Indica
glycos

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heart's

Digoxin binds to the alpha subunit of the Na^+/K^+ ATPase pump i. inhibiting its activity and causing an accumulation of sodium ions within the cell. This in turn leads to a ↓se in the activity of the Sodium / Calcium exchanger, which normally pumps calcium ions out of the cell. As a result intracellular calcium concentration increases which leads to an increase in contractility of the cardiac muscle fibers.

The pharmacodynamic effects of digoxin are dose dependent and can range from positive inotropic effect (increased myocardial contractility) to negative chronotropic effects (↓ heart rate) and antiarrhythmic effects (suppressing certain types of abnormal heart rhythms) The therapeutic range for digoxin is narrow and toxicity can occur with overdose or in the presence of certain drug interaction.

(Q2) Indications and Contraindication for cardiac glycosides.

Na/K^+ pump inhibition

Indication :-

Heart failure - Cardiac glycosides are used to treat heart failure by improving the heart's ability to contract and pump blood

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Date to

effectively.
→ ↓ conduction from atria to ventricle
- Atrial fibrillation - Cardiac glycosides control heart rate becoz in a fib heart beats are irregular.
- Atrial flutter → Cardiac glycoside can also control the heart rate in patients with atrial flutter, a condition where the heart beats too quickly.

Contraindication of Cardiac glycoside :-
- Hypersensitivity
- Ventricular fibrillation - Cardiac glycosides can cause or worsen ventricular fibrillation, a condition where the heart beats rapidly and irregularly
- Contraindicated in patients with Wolff-parkinson-white Syndrome, IInd or IIIrd degree heart block or sick sinus Syndrome
- Electrolyte imbalances → Affect level of potassium, magnesium and calcium in body, which can lead to serious side effects. This medication should be used with caution in patients with Electrolyte imbalances.
- Renal failure

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Q3) Factors that enhance and weaken the effect of cardiac glycosides

- Cardiac glycoside work by ↑ seing the force of contraction of the heart muscle and slowing the heart rate, which can help to improve cardiac function.

* Factor the enhance the effect of Cardiac glycosides :-

- Hypokalemia ⇒ Low level of potassium in blood can Enhance cardiac glycoside effect, because cardiac glycosides block the Na^+/K^+ pumb, and when potassium level are low the pumb become more isensitive to the medication.

- Hypomagnesemia - Mg is required for proper function of the Na^+/K^+ pumb and low mg so it will enhance the activity of cardiac glycoside

- Renal function - Cardiac glycosides are primarily eliminated by the kidney, so impaired renal function can result in higher blood level of the medication, leading to ↑ seed effects.

- Reduced metabolism - The metabolism of Cardiac glycosides can be reduced in

⑥ Antacids :- Antacids containing aluminum or magnesium can ↓ the absorption of cardiac glycoside, reducing their effectiveness.

⑦ Gastrointestinal disorders :- Certain GI disorder such as malabsorption or diarrhea can ↓ the absorption of glycosides, reducing their effectiveness.

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Elderly patients or those with liver disease which can also result in higher blood levels of the medication and increased effects.

* Factors that weaken the effect of Cardiac glycoside :-

① - Hyperkalemia → As the Sodium potassium pump becomes less sensitive to the medication.

② - Hypothyroidism - It can reduce the sensitivity of the heart to cardiac glycosides, making them less effective.

③ - Electrolyte imbalance - Imbalance of electrolyte such as Ca, Na, K. can affect the action of Cardiac glycoside.

④ - Drug interaction - Certain medication such as diuretics and some antiarrhythmic drugs can interfere with the action of cardiac glycosides, reducing their effectiveness.

⑤ - Hypercalcemia - As it can affect the heart's sensitivity to the medication.

(Q4) Methods
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(Q4) Methods for evaluating effectiveness of cardiac glycosides.

→ Clinical assessment is most important method. This involve monitoring the patient's symptoms such as shortness of breath, fatigue, swelling as well as other vital signs such as BP, and heart rate.

- Echocardiography - Evaluate heart function and structure and to monitor changes in response to treatment with cardiac glycosides.

- Serum drug level - Used to evaluate the drug's effectiveness, as higher level may indicate greater drug activity.

- Electrocardiography (ECG) - Changes in ECG can indicate the presence of arrhythmias.

- Exercise tolerance test - Monitoring the patients ability to perform physical activity before and after the treatment.

(Q5) Digitalis Intoxication - Clinical picture.

- Excess of digitalis in body cause Intoxication
- Digitalis is derived from foxglove plant and treat atrial fibrillation and heart failure.

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Symptoms -

- Gastrointestinal Symptoms - Nausea, Vomiting diarrhea and abdominal pain.
- Neurological Symptoms - Confusion, hallucinations, and changes in vision or hearing can occur in severe case of toxicity.
- Cardiovascular Symptoms - Slow or irregular heartbeat, Low BP, Palpitations.
- Other Symptoms - fatigue, weakness, and muscle pain
- In severe cases digitalis toxicity can lead to life threatening complications such as arrhythmias, Seizure and Coma.

Q6) Doctor's Strategy in case of digitalis intoxication.

- Discontinuation of digitalis :- The doctors may need to adjust the patient's medication regimen or find alternative treatment for the underlying heart condition.
- Monitor Vital Signs - Like BP, heart rate, respiratory rate.
- Electrolyte Correction - Digitalis toxicity can

which may require

(Q2)

cause hypokalemia, hypomagnesimia, hypocalcemia. The doctor may prescribe supplements or adjust the patient's diet to correct these imbalances.

- Administration of Antidote → Administer digoxin immune fab (Digibind). This medication binds to excess digitalis in the body and remove it from the system.

- Supportive care - Oxygen therapy, IV fluid help to stabilise the patient's condition.

- Manage arrhythmias ⇒ Digitalis toxicity can cause arrhythmia which may require treatment with antiarrhythmic medication or electrical cardioversion

Diuretics

(Q1) The structure of the nephron and its function. Mechanism of action of Diuretics.

- The nephron is the functional unit of kidney that filters blood and produces urine. Each kidney contains about 1 million nephrons, which consists of the following structure :-

- Glomerulus - a tuft of capillaries where blood is filtered.

- Bowman's capsule - a cup like structure that surrounds the glomerulus and collects the

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filtrate

- PCT - A twisted tube that reabsorbs water, glucose, amino acids, and ions from the filtrate back into the bloodstream

- Loop of henle - A hairpin shaped tube that creates a concentration gradient in the medulla of the kidney, allowing the re-absorption of water and NaCl.

- DCT - A tube that regulates the balance of electrolytes in the body by reabsorbing or secreating ions

- Collecting duct - A tube that carries urine from the nephron to the renal pelvis, where it is excreted from the body.

* The function of the nephron include:-

1) Filtration - By glomerulus.
2) Reabsorption → By PCT and DCT, Loop of henle
3) Secretion → By DCT, and Collecting duct. They secrete excess potassium, hydrogen ion and other waste products into the urine
4) Concentration :- Loop of henle and the collecting duct create a concentration gradient in the

medulla of the kidney, which allows the reabsorption of water and the concentration of urine

* Mechanism of action of Diuretics :-

- Diuretics increase amount of urine produced by kidneys, resulting in increased excretion of water and electrolytes from the body. They are used to treat conditions such as high blood pressure, heart failure and edema. They reduce fluid retention in the body.

Loop diuretics - These drugs such as furosemide and bumetanide, work by blocking the sodium - potassium - chloride transporter in the thick ascending limb of the loop of Henle in the kidney. This prevents the reabsorption of Sodium, chloride and water, leading to a significant increase in urine production.

Thiazide Diuretics - These diuretics such as hydrochlorothiazide and chlorthalidone work by inhibiting the Sodium Chloride transporter in the DCT of the kidney. This reduces reabsorption of Na, Cl and water leading to increased urine output.

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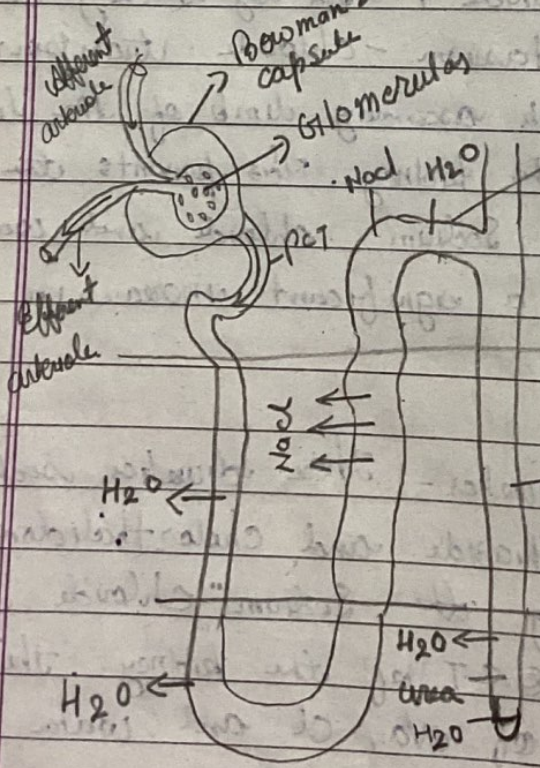
Potassium Sparing diuretics - These drugs such as spironolactone and eplerenone work by blocking the aldosterone receptor in the collecting duct of the kidney. This reduces the amount of Sodium and water reabsorbed but also retain potassium in the body.

Carbonic anhydrase inhibitors - This drugs such as acetazolamide work by inhibiting the Carbonic anhydrase enzyme in the P.C.T. This interferes with the reabsorption of bicarbonate, which leads to increase excretion of bicarbonate, Sodium and water in the urine



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(Q2) Classification of Diuretics, Indication.

Classification is based on site of Action :-

1) Osmotic diuretics
- Mannitol (non specific) - can work anywhere on nephron
* Uses - Angle closure glaucoma
- Cerebral Edema
- Incipient renal failure = Because it ↑s renal blood flow.
- If taken orally - cause osmotic diarrhea.

Contraindication →
- Active cerebral hemorrhage
- Acute renal failure
- Pulmonary edema.

2) Carbonic Anhydrase inhibitors → Acts on PCT.
Indication :-
- Angle closure glaucoma
- Alkalinization of urine
- Mountain sickness (AOC)
- Epilepsy.

* Drug - Acetazolamide
- Brinzolamide } Eye
- Dorzolamide } drops.
→ Acetazolamide
→ Dichlophenamide

3) Loop Diuretics → Acts on thick ascending limb of loop of Henle.
- Inhibits $Na^+ K^+ 2Cl^-$ Symporter
- Drugs - Furosemide
- Torsemide
- Bumetanide
- Ethacrynic acid - Cause ototoxicity
- High efficacy diuretics
- Cause hypocalcemia.

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Indication :-
- Edema (CHF , pulmonary Edema etc)
- Hypertensive emergency
- Bromide and iodide poisoning
- Hypercalcemia.

4) Thiazides - Act on DCT. Increase Ca reabsorption
Drugs : Hydrochlorothiazide
- Chlorthiazide
- Methiazide
- Polythiazide
- Indapamide
- Xipamide
- Chlorthalidone
} Thiazide like diuretics.

Indication :-
- Hypertension (DOC)
- Edema
- Recurrent renal calcium stones
- Bromide and iodide poisoning
- Osteoporosis
- Diabetes insipidus.

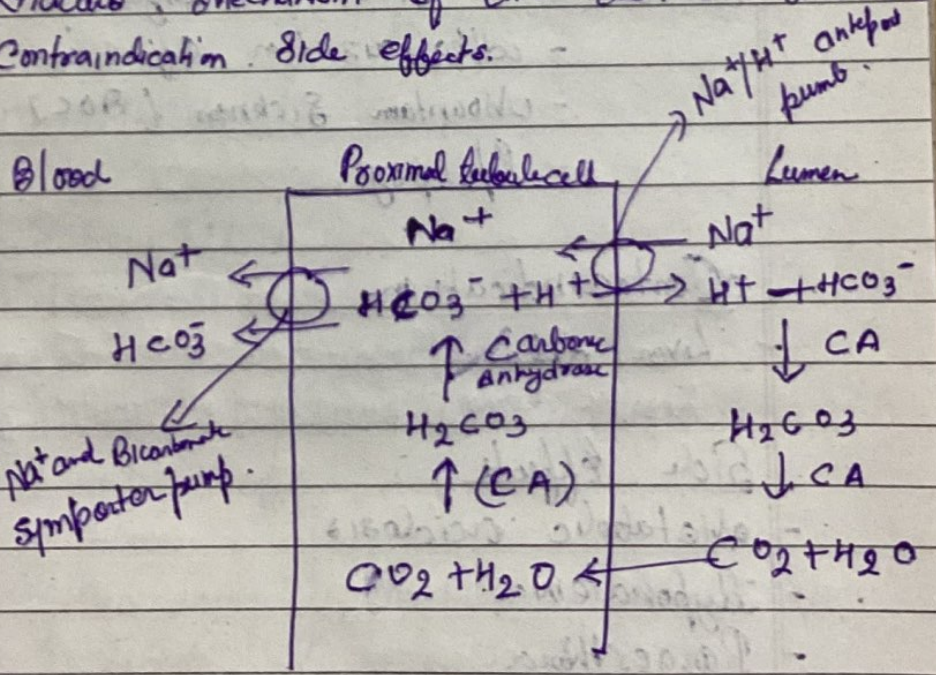
5) K+ sparing Diuretics - Act on Collecting duct

Drugs :-
1) Aldosterone receptor ↓
- Spironolactone - cause gynecomastia because it blocks testosterone receptor
- Eplerenone

11) Epithelial Na^+ channel #
- Amiloride
- Thiamterene

Indication :- Conn's Syndrome (DOC) } Aldosterone antagonist
- Edema in cirhosis (DOC)
- Prevent hypokalemia caused by other diuretics.
- CHF → ↓ LVH.
- Resistant hypertension (DOC)

(12) Diacab, Dichlorphenamide Mechanism of the action. Indication Contraindication Side effects.



- It acts on proximal tubule
- Cause renal stone due to urinary alkalosis
- They are non competitive and reversible inhibitors of carbonic anhydrase enzyme.
- They are weak diuretics.

- Causes loss of Na^+ and HCO_3^- in urine
- Na and H_2O :- Diuretics
- HCO_3 :- urinary alkalosis / Metabolic acidosis
- Have Self limiting action.

Drugs :- Acetazolamide - Given by oral or injectable route.
- Brinzolamide } - Given as eye drops
- Dorzolamide }

Indication :- Glaucoma (Angle closure glaucoma)
- Alkalinization of urine
- Mountain Sickness (AOC)
- Epilepsy

Contraindication:
- Liver disease/Impairment, electrolyte imbalance, hepatic coma, pulmonary obstruction, hyperchloremic acidosis

Side Effects
- Metabolic acidosis
- Hypokalemia
- Paraesthesia
- Renal Stones (Cause due to urinary alkalosis)

(Q4) Thiazide and thiazide like diuretics...

* It is weak diuretics. — Thiazides & Thiazides → Thiazides like diuretics

- Act on distal tubules
- Inhibits Na + Cl⁻ symporter.
- Cause hypercalcemia. (In blood.)
- ↓ Calcium (Hypocalcemia) in kidney.

Drugs :-

- Hydrochlorothiazide
- Chlorthiazide
- Methiazide
- Polythiazide
- Indapamide
- Xipamide
- Chlorthalidone.

} Thiazide like diuretics

* Long acting
* Weak diuretics.

Side Effect.

- ↓ Na^+
- ↓ K^+
- ↓ Mg^{2+}
- ↓ H^+

} ⇒ Release with urine

- ↑ Glucose
- ↑ Uric acid
- ↑ Lipids.

} ⇒ metabolic products

* Thiazide diuretics are preferred in recurrent Renal stones.

* Indication

- Hypertension (DOC)

- Edema
- Recurrent renal calcium stone
- Bromide and iodide poisoning
- Osteoporosis
- Diabetic insipidus → Polyuria → Polydypsia

↓

Nephrogenic DI → (Renal cause)

↓

Doc – Thiazides.

MOA of Thiazides in DI

* Inhibit dilution of urine

↓

Concentrated urine is passed

↓

↓ Plasma osmolarity

↓

↓ Thirst centre ⊖

↓

↓ formation of urine (↓ diuresis)

* Contraindication :-

- Diabetes Mellitus
- Gout
- Hyperlipidemia

Side effect

- → dehydration
- → electrolyte disbalance
  - ↑ uric acid levels
  - Sexual disfunction (erectile ")

(Q5) Loop diuretics. Mechanism of action. Indication, Contraindication. Side effects.

→ Cause hypocalcemia (Blood)

→ Hypercalcemia (kidney)

- Acts on thick ascending limb of loop of henle
- Inhibits Na^+ K^+ $2Cl^-$ symporter

Drugs :- Furosemide
- Torsemide
- Bumetanide
- Ethacrynic Acid - ototoxic.

- They are high efficacy diuretics
- 20-25% of Na^+ is reabsorbed from thick ascending limb of loop of henle

* Indication :-
- Edema (CHF, pulmonary edema, etc)
- Hypertensive emergency
- Bromide and iodide poisoning
- Hypercalcemia.

* Contraindication
- → Diabetes Mellitus
- Gout
- Hyperlipidemia.

* Side effects
- ↓ Na^+
- ↓ K^+
- ↓ Mg^{2+}
- ↓ H^+

→ Release with urine

- ↑ Glucose
- ↑ Uric acid
- ↑ Lipids.

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(Q6) Indication for furosemide :

- Furosemide is a loop diuretic
- used to treat Edema (fluid retention) in CHF, Cirrhosis of liver, kidney disease
- Manage HTN
- Treat high level of calcium in blood

* It works by inhibiting the reabsorption of Na and Cl in the ascending limb of loop of henle (thick part), results in ↑se urine output and ↓se fluid retention.

* Furosemide should be used with caution in patients with certain medical conditions such as diabetes mellitus, gout, electrolyte imbalance, as well as in patients taking certain medication such as lithium and digoxin.

(Q7) Potassium - sparing diuretics. Mechanism of action. Indication, Contraindication, side effects.

→ acts on collecting duct

1) aldosterone receptor blocker

• Spironolactone - cause gynecomastia

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ii) Epith
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Aldosterone come from blood and bind to receptor on lumen of CD

Ther
- ↓N
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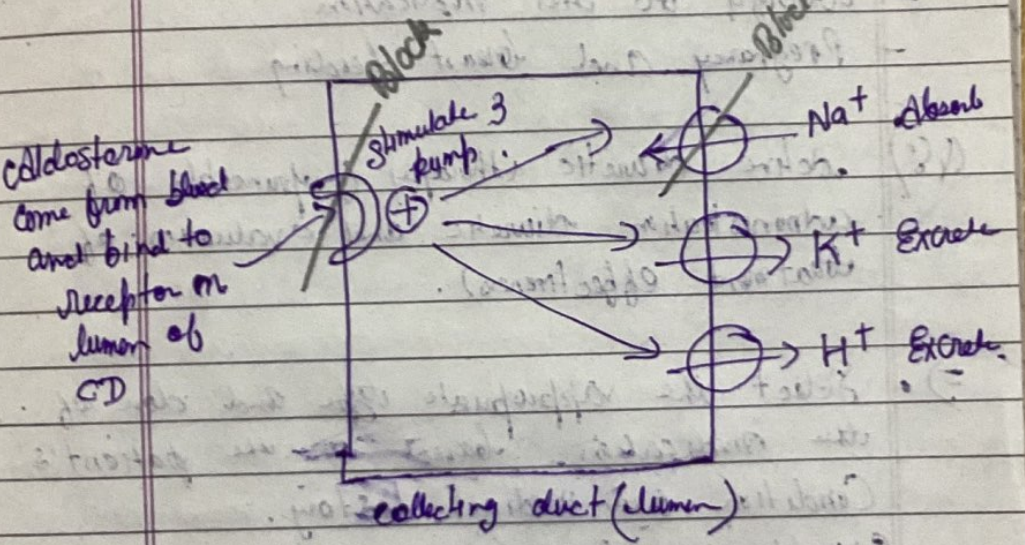
- Res

- Eplerenone
ii) Epithelial Na^+ channel blockers
- Amiloride
- Triamterene.

* All diuretic work from the luminal side except aldosterone antagonist (work from basolateral side

Mechanism of action



There drugs causes :- (Side effects)
- $\downarrow Na^+$ and H_2O - Diuresis.
- $\uparrow K^+$ → Hyperkalemia
- $\uparrow H^+$ → Metabolic Acidosis
- Dizziness, light headedness, Headache, Nausea etc.

Indication
- Conn's Syndrome (DOC) } Aldosterone
- Edema in cirrhosis (DOC) } Antagonists.
- Prevent hypokalemia caused by other diuretics
- CHF → ↓ LVH
- Resistant HTN (DOC)

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Contraindication

- Hyperkalemia
- Severe kidney disease – Because it is eliminated by kidney
- Addison's disease – Because it has low level of aldosterone and the diuretics are aldosterone antagonist
- Allergy to the medication
- Pregnancy and breast feeding

(Q8) Active diuretic therapy (principle of administration diuretic and evaluation of treatment effectiveness).

⇒ • Select the appropriate type and dose of the medication based on the patient's condition and medical history.

Example :-

- Loop diuretics are often used in the treatment of CHF and administer IV for rapid relief.
- Thiazide commonly used to treat hypertension and are taken orally.
- It is important to monitor the patients electrolyte levels particularly potassium, as diuretics can cause potassium loss
- Patients taking diuretics should be advised to consume potassium rich foods or take potassium supplements.

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- The effectiveness of diuretics can be evaluated by monitoring the patient's symptoms and assessing changes in their fluid status. example - use in peripheral edema, SOB, Blood pressure, electrolyte level

- Diuretic typically used in combination with other medication, and life style modification to manage the condition effectively.

- Regular follow up with healthcare provider is also necessary to monitor the response and close adjustment.

(Q9) Maintenance therapy with diuretics (choice of diuretics, the principle of their appointment and evaluation of treatment).

→ Diuretics are commonly used in maintenance therapy for several conditions such as hypertension, heart failure and edema.

→ Loop diuretics such as furosemide and bumetanide are potent and fast acting diuretics that are often used for the treatment of edema associated with heart failure, liver cirrhosis, and kidney disease.

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- Thiazide diuretics such as hydrochlorothiazide and chlorthalidone are milder diuretics that are commonly used to treat hypertension.

- Potassium sparing diuretics such as spironolactone and eplerenone are used to conserve potassium and are often used in conjunction with loop or thiazide diuretics to prevent electrolyte imbalances.

* - The principle of appointment of diuretics involves identifying the underlying cause of fluid retention and selecting the appropriate diuretic based on its mechanism of action, potency, and potential side effects.

- Regular monitor serum electrolyte level because it may cause hypokalemia, hyponatremia
- Monitor renal function.

* - The evaluation of treatment with diuretics involves assessing the patient's response to treatment including reduction in edema or blood pressure, presence of adverse effect

and changes in e

- Of the patient's adverse effect es close may need to to other diureti

(Q10) The choice of d degree of CHF of CHF.

- The choice of diu severity of the c other comorbidi

- For mild to mode as furosemide or

- For severe CHF, and thiazide diu may be necessary Thiazide can enha diuretics.

- In refractory C potassium sparing or eplerenone ma loop diuretics preserve potassium

and changes in electrolyte level.

- If the patient's response is inadequate or adverse effect is significant, the diuretic dose may need to be adjusted or switched to other diuretic.

(Q10) The choice of diuretics depending on the degree of CHF. Guidelines for the treatment of CHF

- The choice of diuretics for CHF depends on the severity of the condition and the presence of other comorbidi

- For mild to moderate CHF loop diuretics such as furosemide or torsemide are often used
- For severe CHF, a combination of loop diuretics and thiazide diuretics such as hydrochlorothiazide may be necessary to achieve adequate diuresis. Thiazide can enhance the effectiveness of loop diuretics.
- In refractory CHF or chronic kidney disease potassium sparing diuretics such as spironolactone or eplerenone may be used in combination with loop diuretics. These medication can help to preserve potassium levels and prevent hypokalemia

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Guideline for the treatment of CHF

* Congestive heart failure is a condition in which the heart is unable to pump blood effectively, leading to fluid buildup. Diuretics are commonly used to treat CHF.
* Loop diuretics are the most commonly used diuretics for CHF

- Start with low dose: Diuretics can cause dehydration and electrolyte imbalance. So it is important to start with low dose and gradually increase it as needed. Monitor electrolyte levels and adjust the dose accordingly.
- Diuretics work best when taken consistently and at the same time daily.
- Monitor weight → Because wt gain is a sign of fluid buildup in case of diuretics
- Monitor side effects such increased urination dehydration, electrolyte imbalance, low blood pressure.
- Follow low salt diet - can help reduce fluid buildup
- Don't stop diuretics without doctor's advice

Suddenly stopping
buildup

Patient
Loop

Assess wt
2H he

wt change < 0.5kg
< 3L / day urine
output

Increase loop
by 50
add metolazone
1.25 - 5 mg
1 to 7 times
a week

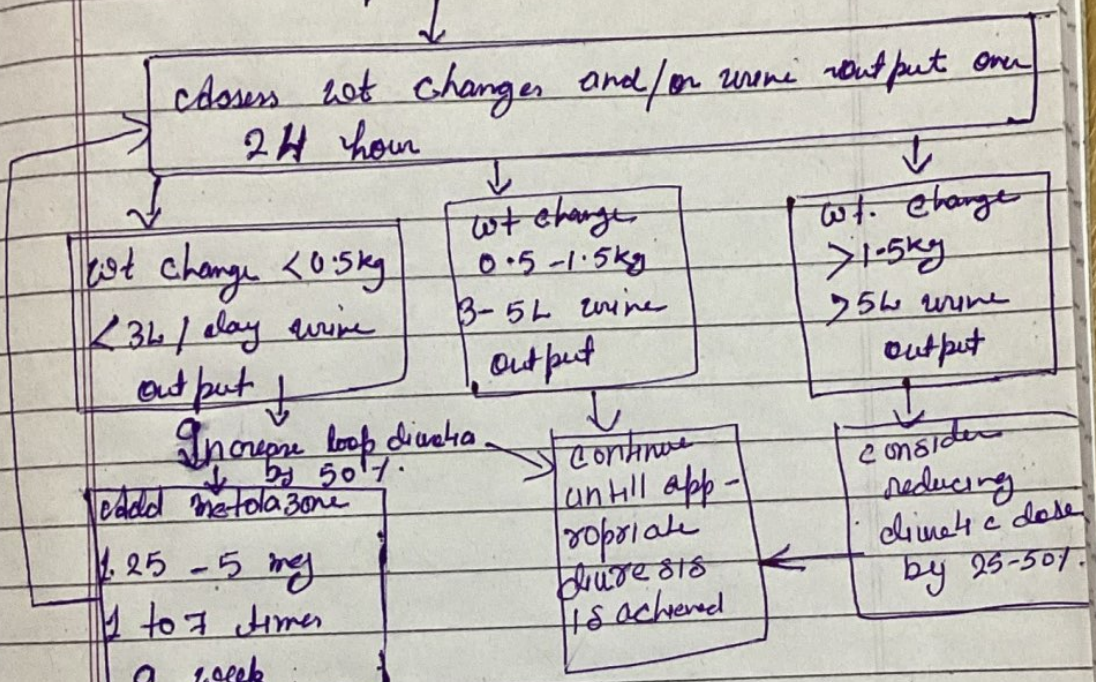
Increasing or
infusion of
or radial in
nephrology

Assume - CI
2) Monitoring
and vigns.
3) Daily weight
4) Urine output
* Titrate

Suddenly stopping a diuretics can cause fluid buildup

Patient with HF and volume overload

Loop diuretic IV dose 20-80 mg/day



Increasing or switching from bolus to continuous infusion of loop diuretics dose, increase metolazone or add inotropic support in conjunction with nephrology or cardiology support.

Assume - (1) Volume assessment with each step
2) Monitoring of electrolyte, renal function, symptoms and vigns.
3) Daily weights.
4) Urine output not often accurate or obtainable

* Titrate progressively according to the degree of

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hypervolemia, furosemide doses and creatinine/kidney function.

(Q11)

NSAIDS → Those agents which are used in the treatment of pain fever and inflammatory is called NSAIDs

(Non steroidal Anti inflammatory Drugs)

- They have following effects :-
  - → Anti-inflammatory → Inhibit COX-II → Arachidonic → PPG (will not convert into)
  - → Antipyretic → Inhibit Peripheral PPG
  - → Analgesics → Inhibit Pain stimuli at sub cortical region (mainly Lloyd COX-II)
    - Inhibit prostaglandin PPG
    - → vasodilation (Hypothalamus)

MOA → Inhibit / Block the COX (II) receptor

They inhibit Synthesis of Prostaglandin by blocking cyclo-oxygenase (COX) enzyme. COX is found in Endoplasmic reticulum of cells

3 type of enzyme → It intact the formation of mucosa of stomach - if COX-1 is absent then there is a chance of ulcer

- COX-I :- It is constitutive enzyme found in stomach (Normal constituent)
- COX-II :- It is inducible enzyme that induce pain inflammation by forming prostaglandins. (generate inflamatory response)
- COX-III :- It is found in brain.

It start the mechanism of pain & inflammation

Primary action :- Peripheral pain Mechanism (main PPG prostaglandin bante hai jisse baad pain/inflam response start hota hai) usko rokne ka kaam karte hai)

NSAIDS

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  - → Analgesics → Inhibit Pain stimuli at sub cortical region → Inhibit prostaglandin PPG → Vasodilation (Hypothalamus) (mainly COX-II)

MOA → Inhibit / Block the COX (II) receptor

They inhibit Synthesis of Prostaglandin by blocking cyclo-oxygenase (COX) enzyme. COX is found in Endoplasmic reticulum of cells

3 type of enzyme →

- COX-1 :- It is constitutive enzyme found in stomach (Normal constituent) (formation of) It intact the mucosa of stomach - if COX-1 is absent then there is a chance of ulcer
- COX-II :- It is inducible enzyme that induce pain inflammation by forming prostaglandins. (generate inflammatory response)
- COX-III :- It is found in brain.

It start the mechanism of pain & inflammation

Primary action :- Peripheral pain Mechanism (main PPG prostaglandin banta hai jisse baad pain/inflam respone start hota hai) usko rokne ka kaam karta hai)

MOA Classification

A. Nonselective COX Inhibitor (traditional NSAIDs)

(max 3g/day) (4-6 hrs)

1. Salicylates: Aspirin (acetylsalicylic acid) 500-1000mg
2. Propionic acid derivative: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen, Dexketoprofen
3. Anthranilic acid derivatives: ~~Diclofenac~~, ~~Aceclofenac~~ Mephenamic acid
4. Aryl-acetic acid derivatives: Diclofenac, Aceclofenac (Phenylacetic acid derivatives)
5. Oxicam derivatives: Piroxicam, Tenoxicam.
6. Pyrrolo-pyrrole derivative: Ketorolac
7. Indole derivative: Indomethacin
8. Pyrazolone derivatives: phenylbutazone, Oxyphenbutazone

B. Preferential COX-2 Inhibitor

- Nimesulide, Meloxicam, Nabumetone (Alkanones)

C. Selective COX-2 Inhibitors (Sulfonilides)

- celecoxib, Etoricoxib, Parecoxib - use for acute pain, Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis

D. Analgesic - antipyretics ∈ poor anti-inflammatory action

1. Paraaminophenol derivative: Paracetamol (Acetaminophen)
2. Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone
3. Benzoxazocine derivative: Nefopam

→ treat Moderate to severe pain, ~~mild~~ can't be but their anti-inflam effects are not strong as other NSAIDs like aspirin, Ibuprofen, naproxen

(1) Nonselective

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(2) Selective

They sel... resp... COX-... Stomach... Selective... pain... rheu...

(3) prefere... resp...

(4) Phar...

→ H can... and its ...

(1) Abso... the gas... depend... administ... most... affect... Topical... effects... While...

(*) ①

→ Nonselective Cox inhibitor

They inhibit both COX-1 & COX-2 enzyme, which are responsible for the production of prostaglandins that cause inflammation, pain & fever.
Nonselective COX-inhibitors are used to treat mild to moderate pain, fever & inflammatory as well as osteoarthritis & rheumatoid arthritis

② Selective COX-2 inhibitor

They selectively inhibit COX-2 enzyme which is responsible for inflammatory, without affecting COX-1 which is imp for maintaining the Stomach lining & preventing bleeding
Selective COX-2 inhibitor are used to treat pain & inflammatory associated ē osteoarthritis rheumatoid arthritis & other condition

③ preferential COX-2 inhibitor

responsible for the production of PPGs that promote inflammation, pain, fever.

(*) Pharmacokinetics of NSAIDs

→ It can vary depending on the specific drug and its route of administration.

① Absorption :- NSAIDs can be absorbed through the gastrointestinal tract, skin or respiratory tract depending on the drug formulation & route of administration. Oral administration is the most common route, and absorption can be affected by food, pH & other factor.
Topical administration can result in local effects without significant systemic absorption, while inhalation can result in rapid system effects

→ for exm the absorption of Ibuprofen may be delayed by food, while the absorption of aspirin may be increased by food.

② Distribution :- NSAIDs are highly protein bound and can distribute to various tissues throughout the body, including joints, synovial fluid & the central nervous system. The extent of distribution can depend on the drug's lipophilicity and ionization.

③ Metabolism :- NSAIDs are primarily metabolized in the liver through various pathways, including oxidation, conjugation, & hydrolysis. The extent of metabolism can depend on the specific drug & its route of administration.

④ Excretion :- NSAIDs & their metabolism are primarily excreted through the Kidneys, either as unchanged drug or as metabolites. Some drugs may also undergo biliary excretion.

If extra

After absorption, NSAIDs are distributed throughout the body and can penetrate into inflamed tissue, where they exert their anti-inflammatory effect. NSAIDs are highly protein bound and are primarily metabolized by the liver through various metabolic pathway, including oxidation, reduction & conjugation.

The elimination of NSAIDs is mainly through renal excretion, with some drugs undergoing entero hepatic recirculation.

The elimination half-life of NSAIDs varies widely with some drugs having short half life (eg- Ibuprofen, with a half life of 2-4 hrs) & other having a longer half life (eg- naproxen, with a half-life of 12-17 hrs)

The pharmacokinetics of NSAIDs can be influenced by various factor, such as age, renal & hepatic function, and the presence of other Medication. Patient

with renal or hepatic impairment may have decreased clearance of NSAIDs, leading to increased risk of adverse effects.

④ Mechanism of Action of NSAIDs

NSAIDs works by inhibiting the activity of cox enzyme (cyclooxygenase), which are responsible for the production of prostaglandins from arachidonic acid. Prostaglandins are lipid signaling Molecules that are involved in a variety of physiological processes, including inflammation, pain & fever.

⇓

There are two isoforms of cox enzymes: COX-1 & COX-2

↓

COX-1 is constitutively expressed in many tissues and plays a role in maintaining normal physiological functions such as gastric mucosal protection & platelet aggregation.

⇓

COX-II on the other hand is induced in response to the production of prostaglandins that contributes to pain, swelling & fever.

⇓

NSAIDs inhibit COX enzyme by binding to active site of the enzyme & blocking the conversion of arachidonic acid to prostaglandins. This leads to reduction in prostaglandin production, which in turn results in decrease in inflammation, pain & fever.

However, some NSAIDs, such as aspirin, have additional mechanisms of action beyond COX Inhibition. Aspirin irreversibly acetylates COX enzyme which leads to a prolonged inhibition of the activity of enzymes involved in synthesis of thromboxane A2, a potent platelet aggregator.

Indications —

⑥ Blood thinning → Aspirin heart attack, stroke by blood clots

① Pain relief :- NSAIDs are commonly used to relief pain of varying degrees, including mild to moderate pain, such as headache, toothache, Menstrual cramps & back pain as well as severe pain, such as post-operative pain & pain associated ~~with~~ cancer

② ~~Inflammation~~ Fever :- NSAIDs are effective in reducing fever, and are commonly used to treat fever associated with various illness, such as the common cold, flu, and other viral infections

③ Inflammation : NSAIDs are used to reduce inflammation in various condition, such as Osteoarthritis, rheumatoid arthritis, gout, and other forms of inflammatory arthritis

④ Dysmenorrhea :- NSAIDs are commonly used to relieve pain associated ~~with~~ menstrual cramps

⑤ Cardiovascular risk reduction :

Low dose aspirin, a type of NSAID, is used for the prevention of cardiovascular events in patients at high risk for heart disease or stroke.

Contraindication

① Known allergy or hypersensitivity to NSAIDs ⇒ who have had allergic reaction to NSAIDs in past should avoid

② Gastrointestinal bleeding or ulcer

③ Children & teenagers ~~&~~ viral infection — can cause Reye's Syndrome causes liver, brain damage in children & teenagers

③ Severe renal impairment - NSAIDs can cause kidney damage, especially in patient ∈ pre-existing kidney disease or reduced kidney function.

④ Pregnancy - NSAIDs can harm the developing fetus, especially when used during 3rd trimester

⑤ History of cardiovascular disease - Some NSAIDs may ↑ the risk of cardiovascular events, such as heart attack & Stroke, especially in patient ∈ pre-existing cardiovascular disease

⑥ Anticoagulant therapy :- NSAIDs can ↑ the risk of bleeding, especially when used in combination ∈ anticoagulant therapy. patient ~~should~~ ~~avoid~~, Anti-coagulant therapy should avoid

Choice of NSAIDs

Depends on various factors, such as the severity & type of pain, patients age & medical history, and potential drug interaction. Some factors to consider when selecting an NSAID include

① Efficacy - The effectiveness of an NSAID in relieving pain & inflammatory is an important consideration.

② Safety - The safety profile of the drug including the risk of gastrointestinal bleeding, kidney damage & cardiovascular events, should be taken into account

③ Selectivity :- Non Selective NSAIDs, such as ibuprofen & naproxen, inhibit both COX-1 & COX-2 enzyme, whereas selective COX-2 inhibit such as celecoxib, selectively inhibit COX-2 ∈ out affecting COX-1. The choice of a selective or non-selective NSAID depends on the

indication & patient's medical history

④ Dosage form - NSAIDs are available in various dosage forms, such as tablets, capsules, creams & gel. The choice of dosage form depends on the site & severity of pain & patient preference

⑤ Cost - The cost of the drug is also a factor to consider especially for long term use

⑥ Drug Interaction - Some NSAIDs can interact with other medications, such as anticoagulants, antihypertensives, & diuretics. The potential for drug interaction should be considered when selecting NSAIDs

Principal of administration

can be administered through various routes, including oral, topical, intravenous, & intramuscular. The choice of administration route depend on the indication, severity of pain, patient age and medical history & potential drug interaction.

① Oral - Oral administration is the most common route of NSAIDs. Tablets, capsules & liquids are available for oral administration. Oral NSAIDs can be taken with or without food, but food can help reduce gastrointestinal side effects

high bioavailability

② Topical - Topical NSAIDs are applied directly to the skin over the affected area. They are effective for localized pain, such as joint pain, muscle strain. Topical NSAIDs are available as cream, gels & patches

③ Intravenous (IV) — IV administration of NSAIDs is used in hospital for the management of severe pain, such as post-operative pain. IV NSAIDs are administered slowly to prevent adverse effect [in case of renal colic]

④ Intramuscular (IM) - IM administration of NSAIDs is used for the management of Moderate to severe pain such as menestrual cramp & dental pain.

The principal of administration of NSAIDs includes -

① Dosage - NSAIDs should be administered at the recommended dosage & frequency. Overdose can lead to serious side effect, such as gastrointestinal bleeding & kidney damage

② Duration of treatment - NSAIDs should be used for the shortest duration possible to minimize the risk of adverse effects

③ Precautions - Patients ₹ underlying health condition, such as liver or kidney disease, should take NSAIDs with caution. Patients should also avoid alcohol, smoking which can ↑ risk of gastrointestinal bleeding

④ Drug Interaction -

Complication of Injectable NSAIDs

abscesses, necrotizing fasciitis, purulent myositis, sepsis

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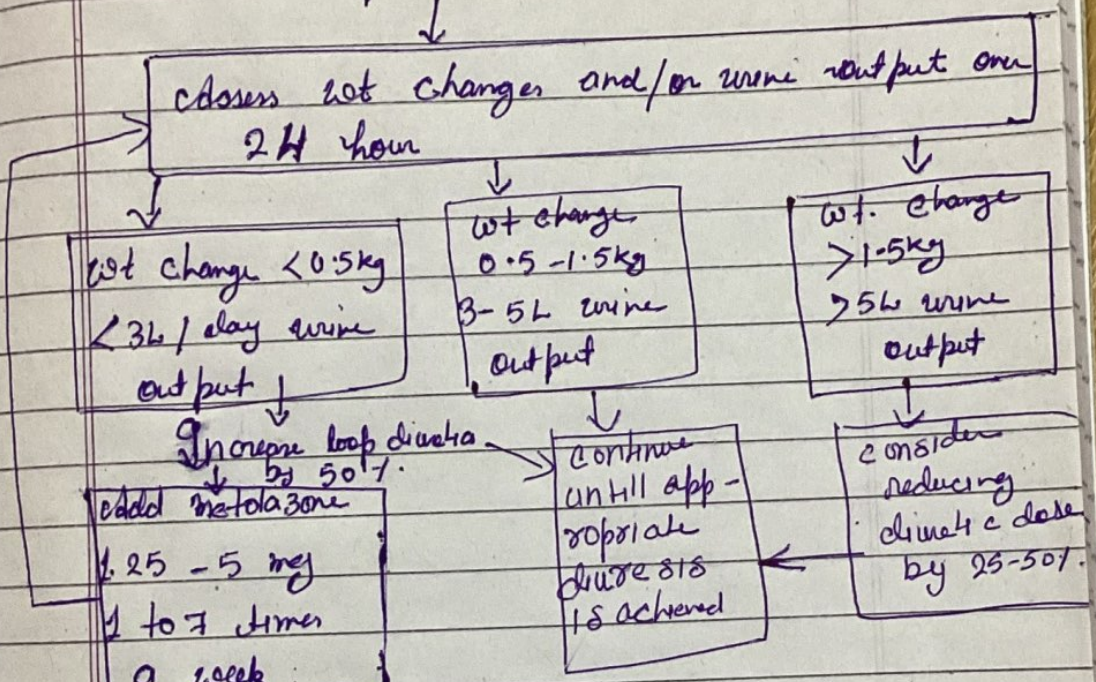
hypervolemia, furosemide doses and creatinine/kidney function.

(Q11)

Suddenly stopping a diuretics can cause fluid buildup

Patient with HF and volume overload

Loop diuretic IV dose 20-80 mg/day



Increasing or switching from bolus to continuous infusion of loop diuretics dose, increase metolazone or add inotropic support in conjunction with nephrology or cardiology support.

Assume - (1) Volume assessment with each step
2) Monitoring of electrolyte, renal function, symptoms and vigns.
3) Daily weights.
4) Urine output not often accurate or obtainable

* Titrate progressively according to the degree of

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Guideline for the treatment of CHF

* Congestive heart failure is a condition in which the heart is unable to pump blood effectively, leading to fluid buildup. Diuretics are commonly used to treat CHF.
* Loop diuretics are the most commonly used diuretics for CHF

- Start with low dose: Diuretics can cause dehydration and electrolyte imbalance. So it is important to start with low dose and gradually increase it as needed. Monitor electrolyte levels and adjust the dose accordingly.
- Diuretics work best when taken consistently and at the same time daily.
- Monitor weight → Because wt gain is a sign of fluid buildup in case of diuretics
- Monitor side effects such increased urination dehydration, electrolyte imbalance, low blood pressure.
- Follow low salt diet - can help reduce fluid buildup
- Don't stop diuretics without doctor's advice

Suddenly stopping
buildup

Patient
Loop

Assess wt
2H he

wt change < 0.5kg
< 3L / day urine
output

Increase loop
by 50
add metolazone
1.25 - 5 mg
1 to 7 times
a week

Increasing or
infusion of
or radial in
nephrology

Assume - CI
2) Monitoring
and vigns.
3) Daily weight
4) Urine output
* Titrate

and changes in electrolyte level.

- If the patient's response is inadequate or adverse effect is significant, the diuretic dose may need to be adjusted or switched to other diuretic.

(Q10) The choice of diuretics depending on the degree of CHF. Guidelines for the treatment of CHF

- The choice of diuretics for CHF depends on the severity of the condition and the presence of other comorbidi

- For mild to moderate CHF loop diuretics such as furosemide or torsemide are often used
- For severe CHF, a combination of loop diuretics and thiazide diuretics such as hydrochlorothiazide may be necessary to achieve adequate diuresis. Thiazide can enhance the effectiveness of loop diuretics.
- In refractory CHF or chronic kidney disease potassium sparing diuretics such as spironolactone or eplerenone may be used in combination with loop diuretics. These medication can help to preserve potassium levels and prevent hypokalemia

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- Thiazide diuretics such as hydrochlorothiazide and chlorthalidone are milder diuretics that are commonly used to treat hypertension.

- Potassium sparing diuretics such as spironolactone and eplerenone are used to conserve potassium and are often used in conjunction with loop or thiazide diuretics to prevent electrolyte imbalances.

* - The principle of appointment of diuretics involves identifying the underlying cause of fluid retention and selecting the appropriate diuretic based on its mechanism of action, potency, and potential side effects.

- Regular monitor serum electrolyte level because it may cause hypokalemia, hyponatremia
- Monitor renal function.

* - The evaluation of treatment with diuretics involves assessing the patient's response to treatment including reduction in edema or blood pressure, presence of adverse effect

and changes in e

- Of the patient's adverse effect es close may need to to other diureti

(Q10) The choice of d degree of CHF of CHF.

- The choice of diu severity of the c other comorbidi

- For mild to mode as furosemide or

- For severe CHF, and thiazide diu may be necessary Thiazide can enha diuretics.

- In refractory C potassium sparing or eplerenone ma loop diuretics preserve potassium

- The effectiveness of diuretics can be evaluated by monitoring the patient's symptoms and assessing changes in their fluid status. example - use in peripheral edema, SOB, Blood pressure, electrolyte level

- Diuretic typically used in combination with other medication, and life style modification to manage the condition effectively.

- Regular follow up with healthcare provider is also necessary to monitor the response and close adjustment.

(Q9) Maintenance therapy with diuretics (choice of diuretics, the principle of their appointment and evaluation of treatment).

→ Diuretics are commonly used in maintenance therapy for several conditions such as hypertension, heart failure and edema.

→ Loop diuretics such as furosemide and bumetanide are potent and fast acting diuretics that are often used for the treatment of edema associated with heart failure, liver cirrhosis, and kidney disease.

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Contraindication

- Hyperkalemia
- Severe kidney disease – Because it is eliminated by kidney
- Addison's disease – Because it has low level of aldosterone and the diuretics are aldosterone antagonist
- Allergy to the medication
- Pregnancy and breast feeding

(Q8) Active diuretic therapy (principle of administration diuretic and evaluation of treatment effectiveness).

⇒ • Select the appropriate type and dose of the medication based on the patient's condition and medical history.

Example :-

- Loop diuretics are often used in the treatment of CHF and administer IV for rapid relief.
- Thiazide commonly used to treat hypertension and are taken orally.
- It is important to monitor the patients electrolyte levels particularly potassium, as diuretics can cause potassium loss
- Patients taking diuretics should be advised to consume potassium rich foods or take potassium supplements.

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Blood ...

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(Q9) Maint...
diuret...
and ...

→ Diuret...
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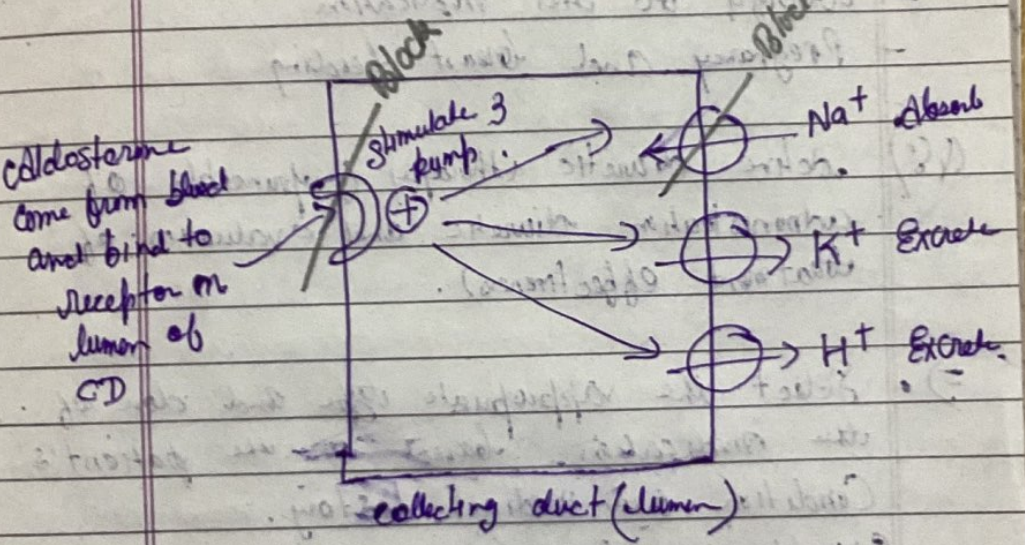
→ Loop ...
taride...
that ...
edema...
work...

- Eplerenone
ii) Epithelial Na^+ channel blockers
- Amiloride
- Triamterene.

* All diuretic work from the luminal side except aldosterone antagonist (work from basolateral side

Mechanism of action



There drugs causes :- (Side effects)
- $\downarrow Na^+$ and H_2O - Diuresis.
- $\uparrow K^+$ → Hyperkalemia
- $\uparrow H^+$ → Metabolic Acidosis
- Dizziness, light headedness, Headache, Nausea etc.

Indication
- Conn's Syndrome (DOC) } Aldosterone
- Edema in cirrhosis (DOC) } Antagonists.
- Prevent hypokalemia caused by other diuretics
- CHF → ↓ LVH
- Resistant HTN (DOC)

Risk factors of adverse effects of NSAIDs

There are several factors that can ↑ the risk of adverse effects associated ē NSAIDs

① Age - Older adults are at ↑ risk of gastrointestinal and renal adverse effect of NSAIDs

② History of gastrointestinal problems -

Patient ē a history ↱ GP, such as ulcer or bleeding are at increased risk of gastrointestinal adverse effect of NSAIDs

③ Renal impairement - Patients ē pre-existing kidney disease or reduced kidney function are at ↑ risk of renal adverse effects of NSAIDs

④ cardiovascular disease - patients ē pre-existing cardiovascular disease, such as heart failure or a history of heart attack or stoke, are at ↑ risk of cardiovascular adverse effect of NSAIDs

⑤ Use of other medications - taking certain medication such as anticoagulant or corticosteroid are at ↑ risk of bleeding & other adverse effect when using NSAIDs

⑥ Prolonged use - Long term use ↱ NSAIDs ↑ the risk of gastrointestinal & renal adverse effects

⑦ Higher doses - Higher doses of NSAIDs ↑ risk of adverse effect.

Adverse effects of nsaids

① Gastrointestinal effects - NSAIDs can cause gastrointestinal adverse effects, including stomach pain, nausea, vomiting, indigestion, and diarrhea. NSAIDs can also cause gastrointestinal bleeding, ulceration, and perforation, especially with long term use or in patient with a history of gastrointestinal problems.

② Cardiovascular effects - Some NSAIDs have been associated with an increased risk of cardiovascular adverse events, such as heart attack & Myocardial infarction, stoke, especially ∈ long-term use of or in patients ∈ pre-existing cardiovascular disease.

③ Renal effects - NSAIDs can cause kidney damage, especially in patients with pre-existing kidney disease or reduced kidney function

④ Skin reactions - NSAIDs can cause skin adverse reactions, including rashes, hives & itching

⑤ Central nervous system effects

NSAIDs can cause central nervous system adverse effects, including dizziness, headache & confusion

⑥ Bleeding - NSAIDs can ↑ the risk of bleeding, especially in patients taking anticoagulant therapy or ∈ history of bleeding disorder

⑦ Allergic reaction - Some patient may have an allergic reaction to NSAIDs which can range from mild skin reaction to severe anaphylaxis

Antianginal Drugs

Nitrates are vasodilators (dilate the blood vessels) that are used to treat angina (chest pain caused by lack of oxygen to the heart muscle) & early the symptoms of congestion heart failure (a chronic progressive condition that affects the pumping power of heart muscle

-> Angina means pain in the chest. This occurs due to decreased blood supply to the heart.

-> It can be of two types

- Stable angina
- unstable angina - is managed just like MI

Stable angina is classified into

(i) Classical angina or Exertional angina
(ii) Variant angina or Vasospastic angina or Prinzmetal's angina

classical angina

Pathophysiology

- When there is atherosclerosis of small branches of the coronary artery the vessels dilates. Due to which the effective diameter ↑ & so the blood supply becomes sufficient, so there is no pain at this site
- When the work of the heart increases due to any stress the heart requires more blood. so the blood vessels of the heart dilates to provide more blood.

→ But the atherosclerosed small vessels is already dialated from before, so it cannot dilate anymore. Now the pain will occur as blood supply will be inadequate

Treatment

- The main mechanism of treatment of angina is to ↓ work of heart

(ii) Variant angina (Pathology)

- It occurs due to vasospasm of blood vessels
- But the trigger of vasospasm is not fixed. So this pain can occur at anytime
- so characteristic feature → Pain at rest
- we can't treat variant angina by ↓ work of heart
- The only treatment possible is vasodilation of the coronary artery.

Drugs used in Angina

1. Nitrates
2. calcium channel #
3. β-blockers
4. potassium channel openers.

1. Nitrates

They act by releasing nitric oxide (NO). It increase cGMP (cyclic guanosine 3,5 - Monophosphate) This cGMP stimulate Protein Kinase - G (PKG) This PKG (Protein Kinase) stimulates the Myosin light chain phosphatase enzyme (MLCP) This enzyme removes the phosphate group which relaxes the muscle & lead to Vasodilation

- Nitrates primarily dilate Veins >> Arteries
- Vasodilation leads to ↓ preload, so used in classical angina
- Nitrates can be used in variant angina also due to dilation of the coronary artery
- Nitrates are broken down by enzyme aldehyde dehydrogenase to form NO. This enzyme is present more in veins. So, NO is produced more in veins

[sublingual, lingual spray, transdermal patch]

Drugs include are

x- Glyceryl trinitrate (GTN / NTG) - sublingual
x- Isosorbide dinitrate (IDN) - sublingual
x- Isosorbide mononitrate (IMN) - oral
x- Pentaerythritol tetranitrate (PETN) - oral
x- Amyl nitrate (AN)

Nitrates have high first pass metabolism, we need to give a high dose if given by oral route

- GTN and IDN are given by alternate route. They are given Sub-lingual as a DOC for Acute attack of angina
- IMN has minimum first pass metabolism
- Longest acting nitrate → PETN
- Shortest acting → AN

Pharmacokinetics & Pharmacodynamics

Organic nitrates are readily absorbed through the buccal mucous membrane, the skin & gastrointestinal (GI) tract. All nitrates except isosorbide mononitrate undergo extensive first pass metabolism, hence oral bioavailability of nitrate is very low.

Sublingual route produces rapid onset (2-5 min) but short duration of Action. Absorption through skin is slow, hence, transdermal route is used for a prolonged effect. The Metabolites are excreted mainly in urine as glucuronide derivatives.

Pharmacodynamics

Mechanism of action

Nitrates act by releasing NO, which causes vasodilation of the smooth muscle in blood vessels, leading to a decrease in peripheral vascular resistance and an increase in blood flow. This reduces the workload on the heart & increases oxygen supply to the heart muscle

Effect on cardiovascular System :-

Nitrates reduce blood pressure, dilate coronary arteries, increase coronary blood flow, and reduce myocardial oxygen demand, thereby improving Systoms of angina

[The primary therapeutic effects of nitrates are the relief of chest pain or discomfort in patients with angina pectoris, as well as the prevention of angina attacks]

Indication

(A) - Angina
- Acute myocardial infarction & acute coronary Syndrome
- Acute heart failure
- chronic heart failure & Pulmonary edema

(B) Biliary colic
(C) Cyanide poisoning
(D) MI (Dil)
(E) Esophageal Spasm
(F) Failure

Use of Nitrates :-

Acute use

NTG is the mainstay of therapy for the Immediate Relief of angina

The most common route of administration is Sublingual (tablets are placed under the tongue) which produces a rapid onset of effect, & avoid liver metabolism (no first pass effect) prior to reaching the systemic circulation

NTG is an unstable compound, & NTG tablets can lose their potency when exposed to heat, light or moisture, and have a limited shelf life. When this happens, typical NTG side effects, such as headache & dizziness are also diminished or lost

Contraindications

- Severe hepatic or renal impairment
- Arterial Hypertension
- The tendency to Orthostatic Collapse
- Increased Intracranial pressure
- Strokes
- Severe anemia
- Aortic & subaortic stenosis
- Mitral stenosis
- Pericardities
- Toxic pulmonary edema
- Glaucoma

contraindicated

Nitrates, as well as those taking medication for erectile dysfunction such as Sildenafil, tadafil or vardenafil The combination of nitrate & these medication can lead to dangerous drop in BP

Nitrates Side effects

- Headache (due to meningeal vasodilation)
- Dizziness, Nausea
- Reflex tachycardia (baroreceptor mediated due to a fall in arterial BP produced by higher doses of NTG)

- Orthostatic hypertension (less common)
- Methemoglobinemia (long-term use of nitrates)
- flushing - Nitrates cause sensation of warmth or flushing, usually felt in the face & Neck
- hypotension
- Nausea & vomiting

Nitrate tolerance

* Prolonged use of nitrates can lead to development of tolerance, where the therapeutic effects of the drug are diminished over time. This is thought to be due to a reduction in the production of NO by the vascular smooth muscle

Nitrate should not be present in the blood for 24hrs a day otherwise tolerance develop

- we need to keep a 6-8hrs nitrates-free period
- if the patient is using transdermal patch we instruct them to remove the patch before sleeping & reapply in the morning

Beta Blockers

Classification of β-blocker

① Non-selective agents (First generation beta blockers)
↓
that block both β_1 & β_2 receptors.

Ex- Propranolol
- Nadolol
- Bucindolol
- carteolol
- Carvedilol
- Labetalol
- Oxprenolol
- Penbutolol
- Pindolol
- Sotalol
- Timolol

② β_1-Selective agents (Second generation beta blockers)

- Acebutolol
- Atenolol
- Betaxolol
- Bisoprolol
- Celiprolol
- Metoprolol
- Nebivolol
- Esmolol

Pharmacodynamics - of β-blocker involves their effect on body. Beta blocker work by blocking the beta receptor in the body, which are responsible for the effect of adrenaline (epinephrine) & noradrenaline (norepinephrine). This results in a decrease in heart rate, blood pressure

and cardiac output. Beta blockers also decrease the release of renin, a hormone that regulates bp. Additionally beta blockers have antiarrhythmic effects and can help prevent angina (chest pain) by reducing the workload of the heart.

pharmacokinetics - of Beta blockers involves their absorption, distribution, Metabolism & elimination from the body. β-blocker are generally well absorbed orally, but their absorption can be affected by food & other medication. They are distributed throughout the body and can cross the blood-brain barrier. Beta blockers are metabolized in the liver & excreted primarily in the urine

- The pharmacokinetics of beta blockers can vary depending on the specific medication. (propranolol 4-6 hrs)
for example, some β-blocker have short half life and require more frequent dosing, whilst others have a longer half-life and can be dosed once daily. (nadolol 20-24 hrs)

- The pharmacokinetics of β-blocker can also be affected by age, liver function and other factors that can affect drug metabolism & elimination.

Withdrawal Syndrome → Abrupt discontinuation of β-blockers can lead to withdrawal syndrome

① Rebound hypertension - the abrupt cessation of β-blocker can lead to sudden ↑ in bp due to ↑ sympathetic activity
② Tachycardia
③ Chest pain & MI
④ Anxiety, agitation & Insomnia
⑤ Nausea, Vomiting, Headache

(6) Feature of β-blocker mechanism of action

Selective β-blocker are type of medication that selectively block the beta 1 receptor in the body these receptors are primarily located in the heart, kidneys & are responsible for regulating heart rate, bp & kidney function.

The mechanisms of action of selective beta blockers involves blocking the effects of the hormone adrenaline (epinephrine) on the beta-1 receptors. By doing so, these medications decrease the heart rate, decrease the force of heart contractions, & low blood pressure. This can be beneficial in condition such as hypertension, angina & heart failure

- Unlike non-selective β-blocker, which block both beta 1 & beta 2 receptor, selective beta blocker have a more specific effect on the heart & are less likely to cause side effects such as bronchoconstriction (narrowing of the airways) in the patient w respiratory condition.

Overall, the selective β-blocker mechanism of action is focused on reducing the workload on the heart, & improving heart function in patient with cardiovascular condition.

lecture

selectivity- the ability to block the β_1 adrenoreceptor of the myocardium selectively
they have a less pronounced negative chronotropic effect.
they reduce the risk of extra cardiac adverse effects:-
① they ↑ the total peripheral resistance in lesser degree, than non-selective BBs
② they reduce the risk of bronchospasm
③ they reduce the risk of hypoglycemia
④ they reduce the tolerance of physical activity in lesser degree, than non-selective BBs

ISA - Intrinsic Sympathomimetic activity - This term is used ē beta blockers that can show both agonism & antagonism at a β-receptor.
Some β-blockers (Oxprenolol, pindolol, penbutolol, labetalol & acebutolol) exhibit ISA. Then agent may be useful in individual exhibiting excessive bradycardia ē sustained beta blocker therapy.

Indications | Agents ē ISA are not used often MI, as they have not been demonstrated to be beneficial. They may also be less effective than other β-blocker in the management of angina!!

- Coronary artery disease ē Angina, Silent Myocardial ischemia, acute myocardial infraction, postinfarction
- Arterial hypertension
- Chronic heart failure (CHF)
- Supraventricular & ventricular arrhythmias
- Delaminating aortic aneurysm
- Hypertropic cardiomyopathy
- Neurocirculatory dystonia

Contraindication

Absolute contraindication

- Prolonged Sinus bradycardia (heart rate less than 50 per min)
- AV blockage (II - III degree)
- Sinus node weakness syndrome
- Bronchial asthma
- Cardiogenic shock
- Hemodynamically unstable CHF
- Hypotension
- DM

Relative Contraindication

- Obstructive pulmonary disease
- Disease ē Severe peripheral circulatory disorder

Adverse effects

Cardiac adverse effects

> Bradycardia (heart rate less than 50 per min)
> AV blockade
> Sinus node weakness syndrom
> Arterial hypotension
> Increasing symptoms of heart failure

Extra-cardiac AE

> Violation of peripheral blood circulation
> Paradoxical hypertensive reaction
> Worsening of bronchial patency
> Reduced exercise tolerance, fatigue
> Hypoglycemia
> Atherogenic shifts
> Sexual violations (Erectile dysfunction)
> Dyspepsia, constipation
Insomnia, unpleasant dreams.

Side effects

- fatigue
- Dizziness, Bradycardia (slow heart rate)
- Low Blood pressure
- cold hand & feet - β-blocker can cause vasoconstriction or narrowing of Blood vessels, which can reduce blood flow to the hand & feet leading to coldness
- Erectile dysfunction
- Bronchospasm
- Nausea or gastrointestinal upset (vomiting/diarr

The commended dosis

Drug	Initial dose (mg)	average therapeutic dose (mg)	max. dose mg/day
① Bisoprolol	1.25 mg x1	10 mg x1	10 mg x1
② Metoprolol	12.5 mg x1	100 mg x1	200 mg x1
③ carvedilol	3.125 mg x2	25 mg x2	25 mg x2
④ Nebivolol	1.25 mg x1	10 mg x1	10 mg x1

Calcium Channel blocker

- Diphenylalkylamine
- Benzothiazepines
- Dihydropyridines

Indications

- coronary spasm, Angina pectoris
- Hypertension
- Hypertrophic cardiomyopathy
- pulmonary hypertension
- Raynaud's phenomenon

Contra indication

- Severe bradycardia
- Sinus node weakness syndrome
- WPW syndrome
- cardiogenic shock
- Severe CHF (except amlodipine)
- Arterial hypotension
- Pregnancy & lactation
- Simultaneous administration of non-dihydropyridine CCBs & BBs
- Aortic & Subaortic stenosis
- Unstable angina & MI for dihydropyridine CCBs

Adverse effect

(#) Effect due to vasodilations

- Headache
- redness of the face, fever
- tachycardia
- arterial hypotension
- tibial swelling

(#) Conduction disturbance
(#) ↑ symptoms of chronic heart failure
(#) electromechanical dissociation
(#) Gastrointestinal disorder — constipation, gum hyperplasia
(#) Muscular weakness

Mechanism

- Decrease in heart function due to
  > post-loading reduction (vasodilation)
  > reducing heart rate & reducing Myocardial Contractility by (for non-dihydropyridein CCBs)
  these lead to ↓ in the myocardial oxygen demand

> Coronary vasodilation.

(#) **Verapamil** → It belongs to a class drugs called calcium channel blockers.
- It primarily used to treat high pressure, angina (chest pain) & certain heart arrhythmia disorder

Positive effects of verapamil

treating
① Lowering blood pressure
② Relieving angina
③ treating of arrhythmias - atrial fibrillation & supraventricular tachycardia

(3) treating certain heart rhythm disorders - Atrial fibrillation
(4) Preventing Migraines
(5) fewer side effects compared to other medications

Negative effects

(1) side effects - Headache, dizziness, fatigue
- Constipation & nausea

(2) Interaction ē other medication - verapamil can interact ē other medication & supplement which can cause adverse effect or make less effective

(3) Worsening heart failure - Verapamil should not be used in patient ē severe heart failure, as it can worsen the condition

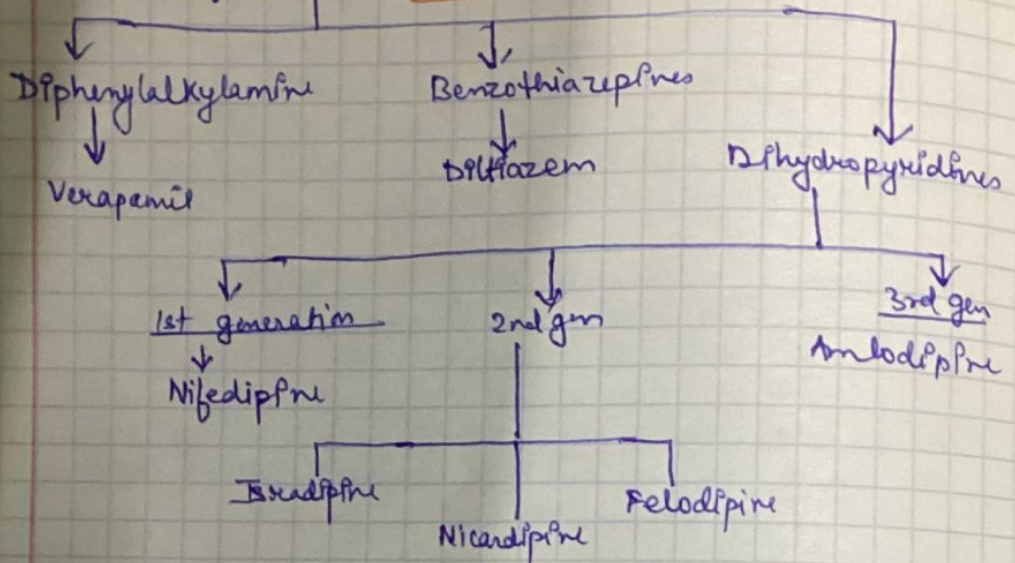
(4) Liver toxicity
verapamil can cause liver toxicity in rare cases, particularly in patient ē liver disease.

NOTE
verapamil primarily affects the cardiovascular system by relaxing the blood vessels, reducing blood pressure, and regulating the heart's rhythm.

→ verapamil was found effective in reducing inflammation in the airways of individuals ē asthma. it has the potential to treat asthma.
And it is also effective in reducing the viscosity of mucus in airway of individual ē cystic fibrosis
(bronchodilator effect)

kidneys are not filtering the blood effectively
chronic kidney disease

Classification CCB



Pharmacodynamics of CCB

- Negative inotropic effect (V > D > N)
- Negative chronotropic effect (V > D), N does not affect the heart rate, can cause tachycardia
- Negative dromotropic effect (V > D)
- Coronary vasodilation (N > D > V)
- 1st dihydropyridines can cause coronary steal syndrome
- peripheral vasodilation (N > D > V)

V - Verapamil, D - Diltiazem, N - Nifedipine

Mechanism of action

CCBs act by inhibiting the influx of calcium ions into cells which reduces smooth muscle tone & cardiac contractility

↓ in heart function due to
- post loading reduction (vasodilation)
- reducing heart rate & reducing myocardial contractility (for non-dihydropyridine CCBs) these lead to decrease in the myocardial oxygen demand
- Coronary vasodilation

Pharmacokinetics →

- Lipophilic drug
- High metabolic beats at the first pass through the liver (the pharmacokinetics of CCB is affected by liver disease)
- strongly bound to a plasma protein
- oral bioavailability from 13 to 25%
- CCB of 1st generation has a short half life (sharp peaks and decrease in the concentration of drugs in plasma
- the maximum action of the 1st generation CCBs take place in 2hrs the duration of the action is 5-6 hrs
- CCBs of the 2nd & 3rd generation are prescribed 1-2 times a day
- verapamil & diltiazem have active metabolites (cumulative effect of the long admission)

Antiarrhythmic (irregular heartbeat)

→ is a problem of the rate or rhythm of the heartbeat as a result of disorder electrical impulse generation & conduction

Causes of Arrhythmia

Heart:- Coronary heart disease, heart valve disease, cardiomyopathy, arterial hypertension etc.
- electrolyte imbalance
- Drugs (antiarrhythmic drugs, cardiac glycosides, antidepressant medication, diuretics) etc.
→ Smoking & alcohol
- Intoxication
- Hypoxia
- PATE (Pulmonary artery thromboembolia)
- Thyrotoxicosis

Mechanism

① Normal & abnormal generation of impulse
② disorder of impulse conduction
③ Disorder of impulse generation & conduction

Classification of antiarrhythmic drugs

① Class I - Sodium channel blockers (prolongs repolarization)
- Class IA - quinidine, procainamide, disopyramide (shorten repolarization)
- Class IB - Lidocaine, Mexiletine, tocainide (little effect on repolarization)
- Class IC - Flecainide, moricizine, propafenone, encainide

② Class II - Beta-blockers
- propranolol, nadolol, bisoprolol etc
esmolol

③ Class III - Potassium channel blockers
- Amiodarone, sotalol, bretylium, ibutilide

④ Class IV - Calcium channel blockers

Verapamil, Diltiazem

⑤ Class V - Miscellaneous group of medication that do not belong to a traditional class of anticoarrhythmics.

- Digoxin - it has +ve inotropic & -ve chronotropic activity

heart failure & ejection fraction

- Adenosine, Magnesium Sulfate, Atropine

[Antiarrhythmic are used to suppress abnormally fast rhythm (tachycardias), such as atrial fibrillation, Supraventricular tachycardia & Ventricular tachycardia]

Tests
① ECG
② 24-hrs Holter monitoring
③ Exercise stress tests

② Sodium channel blockers (1A, 1B, 1C) characteristics

1A

drugs - ① Quinidine
② Procainamide
③ Disopyramide

→ Block the Sodium channels
→ Block potassium channels

Moderate reduce conduction velocity & repolarization
- reduce of Vmax (phase 0)
- increase of APD
- increase of ERP
- negative inotropic effect

ECG
- prolonged PQ, QT interval
- increase QRS duration

1A → Mixed action drug
→ treatment efficacy - average (2+)
→ Proarrhythmic effect - average (2+)
- Torsade de pointes (type of very fast heart rhythm (tachycardia) that starts in heart lower chamber (ventricles))
→ worsening of reentrant arrhythmias

- prolonged QT interval
- Anticholinergic action : ↑ERP, ↑Heart rate
- Negative inotropic effect
- Hypotension after intravenous injection toxicity - (3+)

Pharmakokinetics (1A class)

Parameter	Quinidine	Procainamide	Disopyramide
digestive absorption	80-90%	70-90%	80-90%
protein binding	80-90%	weak 15%	Variable 35-95%
excretion	Liver	Kidney	Liver 60% Kidney 40%
T1/2	5-8 hrs	3-5 hrs	8-9 hrs

Indications =

① Supraventricular arrhythmia

- Paroxysmal AV nodal tachycardia in patient with WPW (Wolff Parkinson white Syndrome) [emergency cardioversion & prevention].
- Atrial fibrillation & flutter in patient (emergency) treatment & prevention

② Ventricular arrhythmia

- High grade ventricular extrasystole & short paroxysms of ventricular tachycardia in patients without hard organic heart disease.
- Paroxysms of sustained monomorphic ventricular tachycardia (emergency treatment)

It is needed to control of proarrhythmic effects by electrophysiological study of heart (EPS).

Quinidine

It is a stereoisomer of quinine, originally derived from the bark of the cinchona tree

Quinidine Sulfate : 300 - 600 mg 4 times a day
tab - 100, 200, 300 mg
tab - extended release 300 mg
cap: 200, 300 mg

Quinidine gluconate: 324 - 972 mg 3-4 times a day
tab extended - release 324 mg
Solution for injection 330 mg/ml

Dosage regimen - 1 intake - 0,1 g (50% of dose)
then 0,2 g every 2 our to daily dose
600 - 900 mg/day, Maintenance dose: 0,2 g 3 times/day

Pharmacodynamics :-

- Heart rate fall
- AV & Interventricular conduction Delay
- Prolong of atrial & ventricular effective refractory period
- ↑ QRS duration & prolonged QT interval
- vagolytic effect of AV node
- Electrophysiological effects are more significant in case of ischemia, hypoxia and tachycardia
- Negative inotropic effect
- Low blood pressure (alpha - blockers effect) especially in case of intravenous intake
- It may cause sinus arrest, AV block, abnormality of automaticity at high doses

Side effects

- Quinnism (Cinchona alkaloid intoxication)
- Diarrhea
- Haemolytic anaemia
- Thrombocytopenia
- Idioventricular rhythm

Rare - drug induced lupus

Contraindication

Congenital long QT interval syndrome
- Torsade de pointes (when two ISTRC points) in past medical history
- AV block, His bundle branch block
- Myocarditis
- Hyperthyroidism
- Psoriasis
- Myasthenia

Procainamide

Pharmaceutical form

Tab and caps - 250, 375 & 500 mg
Tab extended-release 250, 500, 750 mg, 1g
Solution for IV injection 10% - 10 ml
Solution for intramuscular administration 10% - 5 ml

Method of administration
IV injection of 500 - 1000 mg for 10 min

Pharmacodynamics

- Heart rate fall
- Intraventricular & AV (in a lesser degree) Conduction delay
- Prolonged of atrial & ventricular effective refractory period
- ↑ QRS duration and prolonged QT interval
- Vagolytic effect of AV node (in a lesser degree comparing with Quinidine)
- Mechanism of action of major metabolism (N-acetylprocainamide) is similar to amiodarone and bretylium tosylate

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drugs
- Lidocaine
- Mexiletin
- ~~Flecainid~~
  tocain

ECG
- Without Sig
  changes

- Negative inotropic effect (in a lesser degree comparing with Quinidine)
- Low blood pressure, especially in case of intravenous intake

Side effects:

- Arterial hypotonia in case of IV intake
- lupus like syndrome (per os)
- Sickness
- Agranulocytosis

Contraindication:

- Systemic lupus erythematosis
- Torsade de pointes in past medical history
- AV block II – III degree

Characteristics of Antiarrhythmic drug (Class IB)

drugs

- Lidocaine
- Mexiletine
- ~~Fluvalvida~~ tocainide

ECG

- Without Significant changes

- Class Ib drugs slow impulse conduction by producing weak Na+ channel blockade in abnormal tissue (such as ischaemic myocardium) with no effect in healthy tissue
- They do not block K+ channels and have either no effect on repolarisation or may shorten it
- They are only effective for the treatment of ventricular arrhythmias

Lidocaine

- Lidocaine finds use principally for ventricular arrhythmias, especially those complicating Myocardial infarction or occuring, e.g. after cardiothoracic surgery

Pharmacokinetics —

Lidocaine is used IV and has occasionally been used intramuscularly; dosing by mouth is unsatisfactory because its t½ is short (1.5 hr) and the drug undergoes extensive pre systemic (first pass) elimination in the liver

Adverse reactions

are uncommon unless infusion is rapid or their significant heart failure, they include hypotension, dizziness, blurred sight, sleepiness, slurred speech, numbness, sweating, confusion and convulsions

Pharmaceutical forms

Ampuls 2% – 2ml (40mg) · 10 ml – IV
ampuls 10% – 2ml (100mg) – IM
ampuls 1% – 10ml – IV

Solution for intravenous infusion – 40, 100, 200mg/ml – IV by drop infusion

Method of administration

① IV bolus 50–100mg (1mg/kg) for 3 min, then IV by drop infusion 2mg/min, in 10 min
repeat IV bolus – 40–50mg,
in case of inefficiency it is need to increase to 4mg/min
Highest dose – 300mg per 1 hour

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② IM = 600 mg every 3 hrs
③ IV 80 mg in 3 min + 40 mg IM, then 400-600 mg IM every 3 hrs

Mexiletine

- It is similar to lidocaine but is effective orally ($t_{1/2}$ 10 hrs). It has been used for ventricular arrhythmias, espically those complicating myocardial infarction, but is usually poorly tolerated and has been withdrawn in many jurisdictions.

Adverse reactions - almost universal & dose related, include nausea, vomiting, hiccough, tremor, drowsiness, confusion, dysarthria, diplopia, ataxia, cardiac arrhythmia & hypotension

Class 1C (Sodium channel blockade with minimal effect on repolarisation)

- The drugs slow impulse conduction by producing marked Na^+ channel blockade
- They produce weak blockade of some k^+ channel and also block inward Ca^{2+} channel
- There is a minimal effect on repolarisation
- They are effective for the treatment of both atrial & ventricular arrhythmias
- They have significant proarrhythmogenic effect

ECG -

Prolonged PR & QRS

It is rescue medication, bcz they ↑ the risk of death in patient ≥ CHD by 42%

Flecainide

- Flecainide slows conduction in all cardiac cells including the accessory pathways responsible for the Wolff-Parkinson-White (WPW) Syndrome.

- One common indication is indeed where it is the drug of choice is atrioventricular (AV) re-entrant tachycardia, such as AV nodal tachycardia or in the tachycardias associated with the WPW syndrome or similar condition with anomalous pathways.

  - This should be as a prelude to definitive treatment ∈ radiofrequency ablation, which is the overall treatment approach of choice

- flecainide is also very useful in patient ∈ paroxysmal atrial fibrillation, used in conjunction with an agent that blocks the AV node to protect against rapid conduction to the ventricle.

- Flecainide is restricted to patients without evidence of coronary or structural heart disease indeed before it is used an echocardiogram is essential, and in patients at potential risk of coronary artery disease an exercise test or an alternative test of ischaemia is often conducted

- Pharmacokinetics - Metabolism in the liver & renal elimination of unchanged metabolites terminates its action

- The $t_{1/2}$ is 14hrs in healthy adult but may be over 20hrs in patients ∈ heart disease, in the elderly & in those ∈ poor renal function.

- Adverse reactions. Flecainide is contraindicated in patient with sinus node disease, heart failure, and in whose ℰ a history of MI, especially if they have a history of ventricular arrhythmia
- Minor adverse effects include blurred vision, abdominal discomfort, nausea, dizziness, tremor, abnormal taste sensation & paraesthesia

Contraindications

- Atrioventricular block II – III grade
- sick sinus syndrome
- hemifascicular block

Pharmaceutical form ℰ- tablet 50, 100, 150 mg

Usual doses & interval
per os ℰ 50 – 150 mg 2 times a day

Propafenone

- In addition to the defining properties of this class, propafenone has b-adrenoceptor blocking activity equivalent to a low dose of propranolol
- It is occasionally used to suppress non-sustained ventricular arrhythmias in patients whose left ventricular function is normal
- Pharmacokinetics: propafenone is metabolised by the liver & is a substrate for CYP 2D6

Some 7% of caucasian patient are poor metabolisers who, for equivalent doses, thus have higher plasma concentration than the remainder of the population

Adverse reactions are similar to those of flecainide & are commoner in poor metabolism. In addition, conduction block may occur, heart failure may worsen and ventricular arrhythmias may be exacerbated, & propafenone should be used in patient ⊖ sustained ventricular tachycardia & poor left ventricular function.